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TOPIC OF INTEREST - "IAP - IJPP CME 2021"

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IAP - IJPP CME 2021

TECHNOLOGY REVOLUTION IN HEALTHCARE

Bakul Jayant Parekh

Abstract: *Healthcare technology has a profound impact on the delivery of healthcare and its outcomes. The rapid rate of progress in healthcare technologies will accelerate the process in near future. All four areas of technology i.e. diagnostics, monitoring, diagnostic support and public health governance which impact healthcare will show significant development. Artificial intelligence has a major role to play and we shall see the rapid unfolding of an era of doctor-machine collaboration to deliver better outcomes. While healthcare professionals will necessarily need artificial intelligence support to deliver better care, the need for the human intelligence will not go away and the pediatrician will remain centrally relevant for patients. However, to stay relevant, the pediatrician must stay abreast of new technology, adopt it wholeheartedly and reinvent himself periodically.*

Keywords: *Artificial intelligence, Pediatrician.*

Healthcare technology refers to any information technology tool or software designed to boost hospital and administrative productivity, give new insights into medication and therapy, or to improve the overall quality of care provided. Healthcare technology, also known as Health Tech helps to store electronic medical records, gives access to 'Artificial Intelligence (AI)' empowered devices to aid diagnosis and enhances resource management and communication systems. Healthcare technology also provides remote consultation defying distance.

Will artificial intelligence make doctors obsolete?

Artificial intelligence of today should never be equated with general intelligence. AI of today finds patterns in large data pool and use these patterns to attain definitive goals. It extrapolates and calculates facts based on this capability. These qualities make AI relatively better than human intelligence in terms of knowledge based health care system.

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Even though AI would be able to diagnose better and recommend better, significance of the doctors would still exist. Human expertise is required to perform judgement on machine results and in addition patients will need a confident empathetic human being. In order to diagnose switly and efficiently, both human intelligence and artificial intelligence need to work together. As a result, the healthcare outcomes will improve.

There are four areas of technology impact in health care (Box 1).

Box 1. Technology impact in healthcare

- Diagnostics
- Monitoring
- Diagnostic support (support tools for doctors)
- Public health governance

1) Diagnostics and monitoring

With the help of 'health-tech', some complicated and lengthy diagnostic tests will be done in-clinic or at-home at lesser cost and more rapidly.[1] For example, a device that uses spectroscopy to diagnose within 10 seconds without needle prick. It could be a simple clip for the lower lip or a finger pulse oximeter like device which are connected to internet.

We are also seeing the birth of novel technologies like the use of Clustered Regularly Interspaced Short Palindromic Repeats [(CRISPR) - refers to the unique organization of short, partially palindromic repeated DNA sequences found in the genomes of bacteria and other microorganisms] to enable diagnostics at a low cost in an OPD setting.[2,3] Some bioscience companies have already introduced such tests for Covid-19.

A range of wearable devices for monitoring will also be available. For instance, a monitoring device worn by the patients connected to AI on the internet could listen to lung sounds or other symptoms and alert us as soon as symptoms appear. This could be used for a suspected patient of pneumonia. Monitoring devices could also be used for chronic conditions or for patients at risk of a

ischemic heart disease. A wireless worn device connected to the internet could predict or diagnose an impending myocardial infarction or a stroke, hours or even days prior to the attack.

These monitoring devices and technologies will soon be available at OPD and at homes. They will be faster, cheaper and much more accurate than the alternatives available today.[2]

IAP plans

IAP aims to enable early and affordable access to devices and technologies to its member pediatricians by actively identifying such technologies worldwide and enabling affordable access to them. IAP is in the process of partnering with leading universities and institutions in the US and in Europe for this activity. In addition, IAP is working with National Securities Depositories Ltd. (NSDL) e-Gov to create a technology framework for early diagnosis of many conditions by OPD and to enable our member doctors to deliver last mile at-home services using local mobile manpower equipped with AI enabled measurement and monitoring devices.[4]

IAP has already established these early diagnosis and intervention capabilities for four subspecialty areas, namely pediatric cancer, inborn errors of immunity (primary immunodeficiency), dietary (nutrition) assessments, behavioral and neuro development. The health-tech program includes training for pediatricians on red flag signs, access to specialist advice, specialized services, mobile equipment and devices in-clinic and at-home. More information about the service is available at www.smartclinic2.diapindia.org. The program includes a partnership between IAP and the National Cancer Tissue Biobank of IIT Madras, initially for cancer diagnostics and subsequently to be extended across the spectrum of genetic diagnostics and predictive genomics.[5]

2) Diagnostic support

Doctors will have access to computerised diagnostic support at the point of care. The need for such support increases every day due to the extraordinary levels of new knowledge and complexity being continuously added to the practice of medicine.

The computerized support systems use a combination of standard therapeutic guidelines and machine inferred therapeutic guidelines. The diagnostic support results in guided prescription behavior and guided diagnostics, enhancing standards of care, health outcomes and reducing human error.

Plans of IAP for diagnostic support

IAP is engaged in deepening relationships with global leaders in machine aided diagnosis and prescription behavior support - for example companies such as Wolters Kluwer. IAP works with them to enable access to the systems for our member doctors. IAP is also in the process of working with NSDL e-Gov to include diagnostic support into their telemedicine system and into IAP's own IPAN (Indian Pediatric Access Network) OPD digitization system being offered by NSDL e-Gov. (Virtual mentoring, monitoring, and staffing - a new paradigm in remotely managing infection prevention, 2021).[6]

Tools for the practice

Natural language dictation is a tremendous convenience and a tool that will modernize the way doctors use computers. This tool will enable automated local language interpretation and translations. This means that there is no need to write any prescriptions manually. NSDL e-Gov is working to integrate Google natural language and dictation technologies into IAPs own practice management system IPAN and prescriptions.

3) Clinical informatics and public health governance

Electronic medical records (EMR) is the basic data infrastructure on which all progress in public health can be made. EMR is the digital equivalent of paper records, or charts at a clinician's office. EMRs typically contain general information such as treatment and medical history about a patient as it is collected by the individual medical practice. It enables faster access to medical records and histories leading to improved care and enables machine based correlation with historical data, which may be missed by the clinician. Also, aggregated and anonymized EMR data from a widely used system enables availability of epidemiology data for better public health policy and interventions.

Clinical informatics is the information systems using EMR and they result in improved quality through timely, complete and better organized information delivery to the health care provider. They ensure higher productivity by structuring patient care with piped and integrated standard treatment guidelines (STGs), thereby reducing practice variation.

Clinical informatics with EMR facilitate research, education, quality improvement, outcomes assessment and strategic planning. Linking the data with administrative, insurance, educational or multi-institutional databases

provides the statistical power to address previously unanswerable questions.

Remote presence

Going beyond smart phone and sensor strategies, machines are programmed with data on symptoms and from electronic medical records to automate and obviates the need for physical presence of doctors. An example is the FDA approved RP-VITA[7] from iRobot and InTouch Health. This is a medical robot which will be able to make rounds of hospital corridors. Through its use of lasers, sonar and sensors it allows a doctor to examine a patient and interact remotely from anywhere in the world. Autonomous movement is another key feature.[7]

A tricorder for diagnosing pediatric conditions and other benefits of health-tech

We are now on the verge of the pediatrician holding a hand held device like a tricorder with three functions of sensing, recording and computing, which can diagnose most of the common pediatric conditions almost instantly. For e.g. presence of middle ear fluid, respiratory conditions, anemia, jaundice and many more. Health professionals can store, access and retrieve patient information promptly from anywhere and share patient's medical data rapidly, for efficient patient care. Thus health intelligence (AI) has a dual benefit that it enables good data collection and automated intelligent analysis, which in turn facilitates good healthcare.

Health tech in medical education and CME

Going forward, recorded and interactive training will be hybrid. Technology removes the constraints of distance and cost. A leading global expert's course can now reach every doctor on the planet. Expert content delivered digitally and remotely, helped with a local expert or teacher in a classroom or training hospital setting is the future of medical education in both under graduate, post graduate education and continuing medical education for doctors.

IAP digital centre of excellence - The comprehensive teaching institute

IAP's digital teaching offers certificate courses which includes 523 lectures, expert talks identified across 18 sub-specialties, 90+ courses/modules are available for IAP members. Each-topic is supported by an expert advice forum for our doctors. IAP ensures that the content is updated every year to stay current.

IAP education program is created for audiences namely practicing pediatricians, UG students, PG students and other health care personnel (HCP) treating children. Each topic is taught differently depending upon the audience. IAP teaching institute offers live classes with 400+ hours of live teaching every month, also available as an online archive. Over one million attendees (doctors, PG students, UG students) have enrolled in 4 months. Teaching sessions such as lectures, panel discussions, workshops, case study discussions, on-line clinics for doctors are conducted by experts from central IAP, regional and local chapters. Now we have instituted an annual plan of events for all topics across pediatrics, so that doctors can choose which ones to listen at their discretion.

E-PEDICON and PEDIWEEKS

IAP has introduced the E-Pedicon solutions, with five zonal pedicons in 2020. These zonal pedicons were conducted on IAPs online event hosting and management platforms. The entire event is conducted online - from 3-D renditions of the conference area, interactive elements, registrations, support, navigation, exhibition areas, stalls, conference halls, academic sessions, cultural and entertainment events.

Digital technology has transformed healthcare industry and this revolution is expected to continue in the years to come. There seem to be a bright future for health care with the help of advanced technologies such as artificial intelligence, machine learning, deep learning, block chain, healthcare mobile applications, implants and wearables. As long as healthcare organizations and healthcare professionals keep their minds open and create the required infrastructure and systems, there is no saying how far digital technology can go in healthcare.

Because of Covid-19, moving into the digital age very quickly is important. It is better to adapt them than to be left behind. Digitization in office practice is an evolution and not a disruption and investing in digitization is worth the effort.

The healthcare technology decades - A prediction for pediatrics

Technological advancements can be felt in waves, with each wave lasting for a decade

The first wave (2015-2025) will see the following:

- Use of technology for practice automation
- Point of care diagnostics
- Academics: Online discussion forums, case presentation.
- Digital data generation

The second wave (2025-2035) will go further to:

- Treatments driven by artificial intelligence
- A new generation of therapies
- Complete health detail of every child online and adequate technology based referrals

The third wave (2035 onwards) will see independent technologies:

- Autonomous machines that will perform almost all that human specialists do today. Of course, there will always be a human expert to approve!!
- The pediatrician will continue to perform the most important role of oversight.
- Treatment will be more easily available and affordable.

To stay relevant, the pediatrician must reinvent himself every 10 years!

What do people feel? The results of a survey

A survey was conducted by Indian Academy of Pediatrics in 2018-19 with PG students of various colleges participating in it. Responses from 269 participants were analyzed on the current era of education; information was collected digitally. The participants were post graduates across India, 73.2% of the participants were of the opinion that libraries are a necessity in order to have information available at one's fingertips. A majority of 84.6% are in favor of digitization of classrooms. 92% of the participants state that there must be teaching modules for each.

The survey included technological revolution and its awareness. 93.7% of the participants stated that they were aware on the developments in the artificial intelligence. 82.5% of the participants were also aware of deep learning. 86.6% of the participants were of the opinion that medical apps are useful. 70.8% of the participants stated that online consultation for patients would work. Majority (89.2%) of the respondents felt that technology could replace a skillfull specialist in the future. 65.6% were of the opinion that labs are overtaking clinical skills.

The symbiosis of humans and technology

We are entering an era of human-machine collaboration. We must encourage a mutually beneficial relationship wherein we help machines learn and they improve human efficiency. Despite general paranoia over various forms of automation, technology evolves best when it is utilized in conjunction with human labour.

Points to Remember

- ***Healthcare industry is seeing a paradigm shift due to technology revolution.***
- ***Artificial intelligence is coming up in a big way in diagnostics and patient management.***
- ***Embracement of technology is a must for every healthcare person not only for patient management but also for upgrading knowledge.***

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IAP - IJPP CME 2021

SEPTIC SHOCK- FLUID BOLUS DECISIONS AND ASSESSMENT OF FLUID RESPONSIVENESS

***Suchitra Ranjit**
****Rajeswari Natraj**

Abstract: *Circulatory shock is defined as acute cardiovascular dysfunction resulting in inadequate delivery of oxygen and substrates necessary to meet tissue metabolic demand. The history includes pertinent issues related to etiology, such as fever, trauma and gastro-intestinal losses. Clinical examination consists of respiratory mechanics and cardiovascular status including oxygenation, respiratory rate, work of breathing, level of consciousness, heart rate, blood pressure, peripheral perfusion and adequacy of urine output. Laboratory evaluation should include markers of global oxygenation, particularly arterial blood gas, lactate and central venous oxygen saturation. While clinical assessment of perfusion may be sufficient to recognize shock and guide initial management, patients in whom shock is unresolved need further cardiovascular monitoring depending on availability and expertise. Fluid bolus decisions may be guided by dynamic tests of fluid responsiveness which rely on cardio-respiratory interactions, while simultaneously assessing for fluid tolerance.*

Shock management is targeted towards treating underlying etiology and implementation of physiologically based therapies.

Keywords: *Shock, Fluid bolus, Physiology, Responsiveness, Tolerance.*

The basic disorder in septic shock (SS) is inadequate tissue oxygen delivery and/or impaired utilization with variable degrees of altered vascular tone, septic myocardial dysfunction (SMD), relative hypovolemia and deranged regional blood flow.[1,2] As in adults, SS in pediatric age group is predominantly a hyperdynamic state with variable cardiac function [usually elevated cardiac output (CO), low systemic vascular resistance index (SVRI)] with hypovolemia (intravascular volume lost) that may be absolute and/or more commonly relative (intravascular volume redistributed).[3] The cardiac function ranges from hyperdynamic, normal or decreased as in SMD.

The goals of hemodynamic management are restoration of tissue perfusion in order to prevent organ dysfunction and therapy typically includes fluid resuscitation and vasoactive therapy.[1]

The Pediatric Surviving Sepsis Campaign (pSSC) guidelines have given a broad outline for the hemodynamic management of septic shock.[1] However, wherever possible and considering the complex pathophysiology, therapeutic strategies should address the physiological derangement in an individualized manner. Though clinical examination is important to diagnose the shock state, this alone cannot be relied upon to pinpoint the precise hemodynamic management.[2] For instance, while shock may be readily recognized in a patient with tachycardia and cold mottled extremities, this information is insufficient to identify the cause and therefore to guide the precise initial hemodynamic therapy.

Hemodynamic monitoring

In patients with unresolved shock despite initial therapies, invasive arterial blood pressure (IBP) monitoring is important to diagnose as well as categorize shock. Mean arterial pressure (MAP) is the upstream pressure for perfusing vital organs. Targeting MAP between 5th and 50th centile is required to optimize macrocirculation, with the higher range preferred for patients with concomitant neurological pathology. Vasodilatory shock is diagnosed by either diastolic BP (DBP) less than or equal to half the systolic BP or a pulse pressure above 40 mm Hg with tachycardia and warm extremities. Narrow pulse pressure (pulse pressure less than 40 mm Hg) with cold peripheries indicates vasoconstrictive shock which is typical in hypovolemic or cardiogenic shock.[3]

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Assessment of circulating volume and physiologic rationale of fluid administration

Some degree of hypovolemia may be present in the majority of critically ill children with hypoperfusion irrespective of the etiology, including those with sepsis and septic shock. However, the clinical determination of the intravascular volume can be extremely difficult especially in children without overt large volume fluid losses and in these patients fluid boluses must be administered with great caution rather than being reflexive.[4] This is because fluids can have detrimental consequences in some including increased cardiac filling pressures and eventually fluid overload, exacerbation of septic endothelial damage and vasodilation which can prolong the duration of mechanical ventilation, length of PICU and hospital stay. Also increases the need for pressors and increases the mortality of critically ill patients.[5-8]

In septic shock, hypovolemia may be absolute (blood volume lost) or more often relative (blood volume redistributed); in both cases, the circulating blood volume is insufficient to maintain vascular wall tension, mean systemic filling pressure, venous return, cardiac filling, cardiac output and arterial blood pressure. While fluid expansion can restore a higher mean systemic filling pressure even in vasodilatory shock, the pathophysiological mechanisms suggests that early consideration to restore the vascular tone with vasoactive agents may also be important.[9]

Recent reports on septic shock in children and adults indicate that only a proportion of patients who receive a fluid challenge are fluid responsive (FR) with a demonstrated increased stroke volume (SV) or cardiac output (CO), further, the increase may not be sustained.[10] After the initial 10-20 ml/kg of fluid bolus (FB), clinicians should attempt to predict fluid responsiveness, whether further volume will improve the patients preload or cardiac output.[11,12]

Fluid responsiveness can be assessed through static variables, such as central venous pressure (CVP), HR and global end-diastolic volume index or by dynamic tests, such as arterial pressure variations that result from heart-lung interactions during mechanical ventilation (Fig.1). Although CVP a static variable, which poorly reflects intravascular volume in adults and children, is often used to guide fluid therapy in critically ill patients.[13-15] Fluid boluses that aim to achieve an arbitrary CVP value may not be physiologically rational, since in a healthy person, the CVP is close to zero and therefore a significant CVP elevation after fluid administration should be interpreted as an early sign of right ventricular (RV) dysfunction. Giving more fluids beyond this point could worsen cardiac function and impair venous return and tissue blood flow. Therefore, changes in CVP can be helpful to monitor the response to fluid therapy and a rise in CVP may be more useful as a stopping rule (safety end-point) rather than a target for volume resuscitation.[16] The CVP is also influenced by thoracic, pericardial and abdominal pressures, further complicating it's use as a marker of intra-vascular volume.[15]

Over the last two decades, several dynamic tests of fluid responsiveness have been developed. These tests use heart-lung interactions and are based on the principle of inducing brief changes in cardiac preload and then observe for an improved CO. If the stroke volume (SV) or CO increases more than 10-15% from baseline, the patient is considered to be on the steep part of the Frank-Starling (FS) curve (Fig.1) and is fluid responsive. Patients in whom the increase in SV or CO is less than 10-15% are considered to be on the flat portion of the FS curve and are fluid nonresponsive, therefore administered fluid may merely contribute to increased lung fluid rather than improve the hemodynamics.[11,12]

Examples of dynamic tests for fluid responsiveness include systolic pressure variation (SPV), pulse pressure variation (PPV) and stroke volume variation (SVV). Currently these are the most reliable techniques of assessing fluid responsiveness.[11] These are based on heart-lung interactions leading to respiratory variations in stroke volume that are exacerbated in hypovolemia.

Pulse pressure variation (PPV) is a reliable and readily available dynamic test to assess fluid responsiveness, with PPV of >12% indicating a FR state (PPV= PP max - PP min/ PP mean x 100). While considered more reliable than static variables to guide fluid responsiveness, the performance of dynamic tests requires rigid criteria (mechanical ventilation with tidal volumes (V_T) of at least 8 ml/kg, no spontaneous breathing, absence of right ventricular dysfunction, etc.). It is unusual for all these criteria to be fulfilled in typical ICU patients whenever a fluid bolus is deemed necessary and these tests although physiologically attractive, may not be practically useful.[11]

Other tests such as passive leg raise (PLR), although easy to perform even in spontaneously breathing patients, needs CO measurements to demonstrate SV or CO increments.[11]

Fluid administration that is guided by clinical examination and dynamic tests may help the clinician at

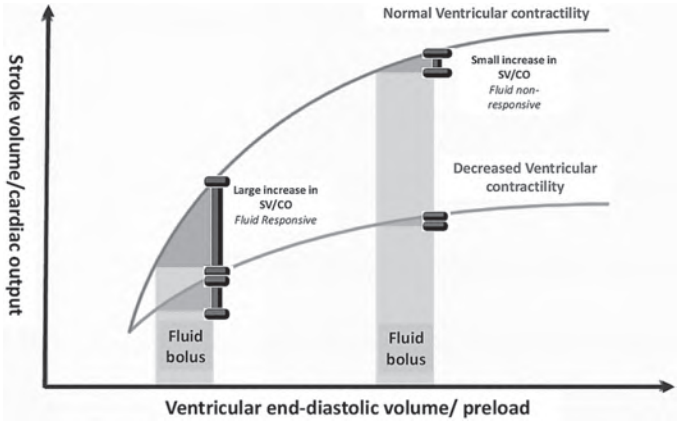

Fig.1. Frank-Starling curve - Concept of fluid or volume responsiveness

Response to fluid bolus in patients with normal and decreased ventricular contractility. In fluid-responders, following a fluid bolus, the increment in stroke volume / cardiac output is >10-15% and in non-fluid responders, the increment in stroke volume/cardiac output is <10-15%. The corresponding increments are less in patients with decreased ventricular contractility

SV: Stroke volume, CO: Cardiac output

bedside to make risk-benefit considerations in a physiologically rational way and can minimize fluid overload and other detrimental consequences of excess fluid. Unfortunately, these tests are reliable only under strict conditions that are rarely met by typical ICU patients and these include controlled mechanical ventilation with tidal volumes at least 8 ml/kg, no spontaneous breathing, absence of right ventricular dysfunction, open chest and intra-abdominal hypertension. Moreover, dynamic tests often require an accurate and objective measure of cardiac output measurement to document efficacy which may not be available in many settings.[11]

However, it is important to remember that being fluid-responsive is a physiologically normal state and not all patients who are fluid responsive need fluid bolus unless they have features of shock. Even in the presence of shock, fluid-responsiveness should not trigger automatic fluid boluses in a patient with oxygenation defects and abnormal lung mechanics. Fluid boluses can result in vasodilatation and decreased organ perfusion pressures in some patients.[7,8] Alternative strategies to improve hemodynamics in vasodilatory septic shock after an initial small volume fluid bolus include the earlier initiation of vasoactive agents. In vasodilatory shock, ino-pressors can potentially improve venous return even in fluid-responsive patients by mobilizing circulating volume that is redistributed in the expanded venous capacitance vessels by converting unstressed to stressed volume. Early low dose norepinephrine in septic shock has been shown to decrease fluid requirement, the duration of ICU stay and the need for rescue technology such as mechanical ventilation, without worsening organ function.[9]

Points to Remember

- ***In a child with shock, the history must include pertinent issues related to etiology such as fever, trauma, gastro-intestinal losses.***
- ***Clinical evaluation includes assessment of respiratory mechanics and cardiovascular status, including oxygenation, respiratory rate, work of breathing, level of consciousness, heart rate, blood pressure, peripheral perfusion and urine output.***
- ***After initial stabilization and initial 10-20 ml/kg fluid bolus, further fluid boluses should ideally be based on tests of fluid-responsiveness.***

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CLIPPINGS

A cross-sectional study of enteric fever among febrile patients at Ambo Hospital: Prevalence, risk factors, comparison of Widal test and stool culture and antimicrobials susceptibility pattern of isolates.

The objectives of this study were to: 1) estimate the prevalence of enteric fever among febrile patients visiting hospital; 2) comparison of Widal test and stool culture; 3) evaluation of the antimicrobial susceptibility of isolates; and 4) assess potential risk factors to acquire enteric fever infection. Blood and stool samples were collected from 372 febrile patients with symptoms clinically similar to enteric fever. Widal test was used for testing sera while stool culturine and bacterial identification was done using WHO standard methods. Susceptibility testing was done using Kirby-Bauer disc diffusion method. The apparent and true prevalence of enteric fever were 56.2% (95% confidence interval [CI]: 50.97-61.29%) and 57.52% (95% CI: 52.3-62.6%) respectively, while, the culture prevalence was 2.7% (95% CI: 1.30-4.89%). Isolation rates of S. Typhi and S. Paratyphi were 0.8% (95% CI: 0.17-2.34%) and 1.9% (95% CI: 0.76-3.84%) respectively. The isolates showed 100% resistance to amoxicillin, bacitracin, erythromycin, 80% resistance to cefotaxime and streptomycin and 20% for chloramphenicol. The sensitivity, specificity, positive and negative predictive values of Widal test was 80.0, 44.5, 3.8 and 98.8% respectively. Multivariable logistic regression analysis revealed that age (adjusted odds ratio [aOR]=2.45; 95% CI: 1.38–4.37; *P*=0.002), religion (aOR=15.57, 95% CI: 3.01-80.64; *P*=0.001), level of education (aOR=2.60, 95% CI: 1.27-5.28; *P*=0.009), source of water (aOR=2.20, 95% CI: 1.21-3.98; *P*=0.009), raw milk (aOR =2.19, 95% CI:1.16-4.16; *P*=0.016) and raw meat consumption (aOR=1.80, 95% CI: 1.07-3.01; *P*=0.026) are the predictors of enteric fever seropositivity. Patients were wrongly diagnosed and treated for enteric fever by Widal test. Therefore, rapid tests with better sensitivity and specificity are needed for the diagnosis of enteric fever. Provision of safe water, health education and behavioral change towards raw food consumption are vital for prevention.

Deksissa T, Gebremedhin EZ. A cross-sectional study of enteric fever among febrile patients at Ambo hospital: prevalence, risk factors, comparison of Widal test and stool culture and antimicrobials susceptibility pattern of isolates. BMC Infect Dis 19, 288 (2019). https://doi.org/10.1186/s12879-019-3917.

IAP - IJPP CME 2021

FUNDUS EXAMINATION

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****Sailatha Ganesh**
*****Praveen Krishna R**

Abstract: *Childhood blindness is a major cause of concern and its late diagnosis and treatment can lead to visually challenged adults causing an economic and social burden to the society. Not only parents and caregivers but also pediatricians and ophthalmologists have a collective role in giving better visual potential to the children. The appropriate antenatal and postnatal history along with a good clinical examination is the key for further management. Fundus examination plays an important role in diagnosis and prognostication of many systemic pathologies. Hence, it is recommended for all children to undergo visual assessment, external oculofacial examination, distant direct ophthalmoscopy and a dilated fundus examination. The Rashtriya Bal Swasthya Karyakram of the Government of India stresses on universal eye examination of all newborns to detect preventable causes of blindness.*

Keywords: *Fundus examination, Systemic association, Ophthalmoscope, RetCam, Retinopathy of prematurity, Children.*

Eye examination in a child is crucial and also challenging for the parents and ophthalmologists. The antenatal history to rule out TORCH infections, perinatal history, complications and the developmental milestones of the child should be carefully taken. External examination including oculofacial anomalies, head posture, external eye structures should be the initial part of eye examination.[1]

Fundus is the part of any hollow organ that is farthest from its opening. For example, fundus of stomach, bladder, uterus, etc. The fundus in the eye includes the retina, macula, fovea, optic disc and blood vessels, choroid and sclera. This article deals with detailed description of fundus examination techniques and its importance with systemic associations in children.

Fundus or retinal examination can be done by 1. direct ophthalmoscopy, 2. indirect ophthalmoscopy and 3. retinal imaging by a fundus camera.

1. Direct ophthalmoscopy

It is carried out with a direct ophthalmoscope which consists of a metallic optical tube, usually made of a durable light weight metal such as chrome-plated brass for proper alignment of the contents. Inside this tube, there is a glass condensing lens, objective lens, mirror/prism aperture dial assembly, red-free/polarizer assembly and lamp that are sealed.[2] The aperture dial is mounted such that it maintains alignment despite a fall/accidental drop from a reasonable height. Fig.1 shows the instrument parts and Fig.2 shows its various apertures.

The apertures are:

1) Small spot: This provides approximately a five degrees cone and is used for a small pupil. It also helps decrease corneal reflexes and increases patient comfort.

2) Large spot: This provides an approximately eight to ten degrees illuminated circle (though highly dependent on the refractive status and pupillary diameter).

3) Fixation star: Accurate eccentric fixation testing, disc assessment and retinal mapping

4) Cobalt blue spot: Examination of corneal abrasions and scarring

5) Red free filter: To detect changes in nerve fibre layer and observe for microaneurysms and vascular abnormalities

6) Macular spot/pinhole: This provides a small spot to observe only the fovea/macula without any undue light thereby minimizing patient discomfort and enabling viewing through a 1-2 mm pupil.

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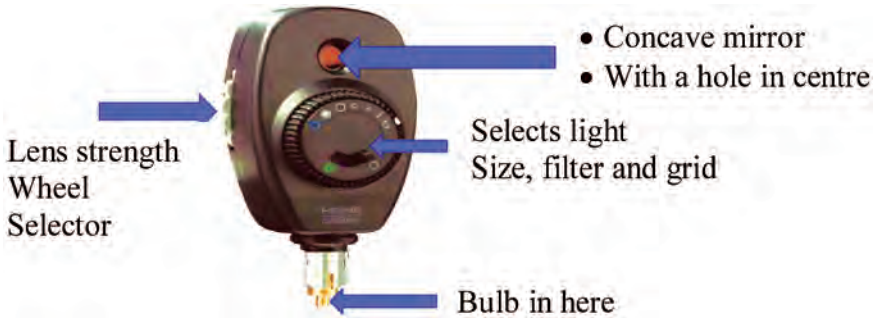

Fig.1. Parts of direct ophthalmoscope

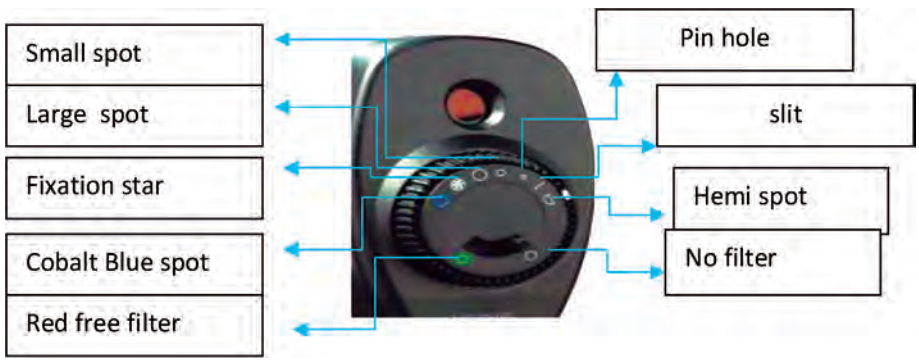

Fig.2. Apertures of direct ophthalmoscope

7) Slit: Accurate assessment of retinal elevations and depressions. Assessment of anterior chamber depth.

8) Hemi-spot: Reduces corneal reflex and provides retinal depth perception.

Steps of direct ophthalmoscopy

There are five steps to perform a complete direct ophthalmoscopy. The patient should be seated in a semi-dark room and instructed to look at a distant target. Examiner stands on the right side of the patient and holds the ophthalmoscope with the right hand to examine the patient's right eye. For the left eye examination examiner stands on the left side of the patient and holds the ophthalmoscope in the left hand.

First step: It is to do examination at 1metre distance. This sheds light on any abnormalities of the eyelids, orbit and periorbita as well as highlights any obvious ocular deviations.

Second step: This is followed by a distant direct examination at 22-25 cm. It is useful to see any media opacities in the lens, cornea and vitreous. This examination shows a red reflex and highlights any opacities in the media as black images. The patient is asked to look in the four cardinal gazes and the movement of the opacity noted. Movement against the ocular movement means the opacity is behind the nodal point of the eye (i.e. in the lens or vitreous) while movement with ocular movement would indicate corneal or anterior opacity. This is called displacement by parallax method.[2]

Third step: Examiner moves closer to the patient and correspondingly increases the power in the condensing lens to examine the magnified anterior segment structures in detail.

Fourth step: The condensing lens power is reduced such that any part of the retina comes into focus. While reducing the power, the vitreous cavity comes into focus and any pathology in it may be seen. Once the retina is focused, the blood vessel is localized and it is followed backwards against the branching pattern to reach the optic disc, then moved temporally from the disc to reach the macula.

Fifth step: The patient is asked to look into the light bringing the fovea into focus, then vessels can be traced into the periphery from the disc to reach second and third order vessels. This completes the posterior pole examination and to examine the periphery the patient is asked to look in the four cardinal gazes while continuing to focus the retina.

Bruckner's test

In a darkened room the child should be seated at the same eye level as the examiner. For a toddler it is better to make the child sit on the parent's lap (make sure infant is not sleeping). The pediatrician/examiner looks through the ophthalmoscope using the lowest light and focuses on the iris, while the patient is asked to fix on the light of the ophthalmoscope.

Therefore it is recommended to conduct the test from a close distance (0.2 to 1 m or 2 to 3 feet) and visualise both eyes simultaneously.

In normal children, both pupils shine equally while in pathological conditions they shine differently. For e.g., in squint there is increased light reflex in the deviated eye, punctuate lens opacities or diffuse lens clouding can be noted in congenital cataract. Leukocoria (white pupillary reflex) is a serious condition which needs to be addressed immediately.

In Bruckner's test one must also look for central steady maintained fixation (CSM); when the light falls on the child's eye the examiner assesses whether the corneal reflex in both eyes is central or deviated. When the child is able to fix on the source of light steadily and is able to maintain fixation on uncovering each eye alternatively the reflex is said to be steady and maintained respectively.

Testing of the red reflex

In the neonates, infants and children, testing of the red reflex by the pediatrician using a direct ophthalmoscope is very important. They have to be trained to do this test which will help in early referral of the child who has any ocular pathology. This method of opportunistic screening has advantages over a population-based screening to reduce childhood blindness burden.

2. Indirect ophthalmoscopy

This is carried out with an indirect ophthalmoscope which consists of a headband, binocular lens with mirrors and a light source. The examiner wears the device by positioning the headband around the head so that the binocular lenses sit directly in front of their eyes. Hand held "condensing lens" is held by the examiner, a few inches above the patient's eye (Fig.3). The purpose of this lens is to "gather" the light rays coming out of the patient's eyes which are divergent due to the power of the cornea.[2] It is useful as a diagnostic tool to examine the retina and therapeutic as in laser indirect ophthalmoscopy to treat retinopathy of prematurity (ROP). The diluted

Fig.3. Indirect ophthalmoscopy technique

dilating drops tropicamide 0.5% and phenylephrine 2.5% are applied times at 10 minutes interval (one drop in each eye).

3.Retinal imaging with a retinal camera

Retinopathy of prematurity is a very important cause of childhood blindness and the gold standard for diagnosis of ROP is indirect ophthalmoscopy.[3] Babies with a birth weight less than 2,000 g and less than 34 weeks gestation should be screened by an ophthalmologist before discharge from NICU or within 30 days after birth whichever is sooner.[3] The role of pediatrician is very important in terms of referral to an ophthalmologist within this crucial time period.

In recent years, retinal imaging by a fundus camera (for example: RetCam, Neo) has become a validated and accepted model of ROP screening (Fig.4). The RetCam or the Neo is a portable wide field digital imaging system that captures ophthalmic images of premature infants. Images are then seen by the ophthalmologist or graded by certified technicians and further treatment or observation is decided by them.[4] This is very useful in rural areas and poor economic background where there are not many trained ophthalmologists which results in many of these babies from getting screened and treated for ROP.

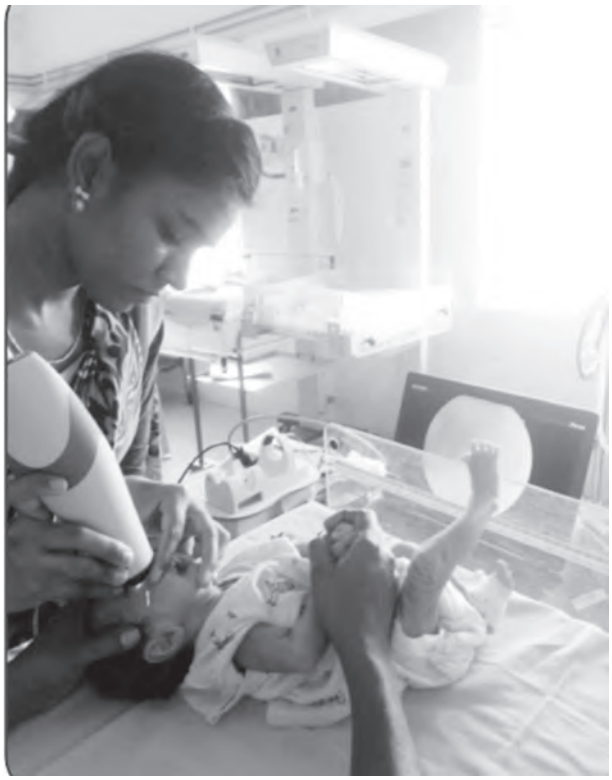

Fig.4. RetCam screening in progress

Training technicians in operating and correct usage of RetCam helps in early identification of ROP in children and makes way for reducing preventable blindness in these tiny babies.[5]

The fundus examination gives the pediatrician and ophthalmologist an invaluable insight into many associated systemic conditions.

a) Tubercular choroiditis is the most common manifestation of tubercular uveitis;[6] it could be multifocal or focal choroiditis. Tuberculoma, retinal vasculitis and panuveitis are the other manifestations. Fig.5a shows picture demonstrating TB multifocal choroditis bilaterally and Fig.5b shows choroidal granuloma.

b) Meningitis: papilloedema is the most common fundus manifestation in TB meningitis followed by papillitis.[7]

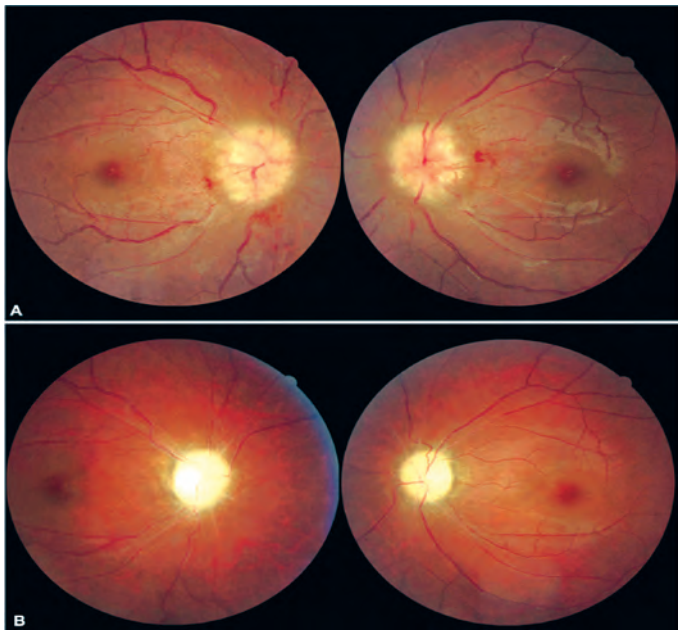

Fig.6. Papilloedema and secondary optic atrophy

Blindness is due to secondary optic atrophy post papillodema /papillitis either complete (temporal optic disc pallor) or complete (total optic disc pallor). Fig.6 shows papilloedema and secondary optic atrophy.

c) Raised ICP: fundus findings are papilloedema and secondary optic atrophy. Peripapillary flame hemorrhages, venous engorgement and hard exudates are features consistent with acute papilledema.

d) Space occupying lesions: fundus examination shows papilloedema.

e) Optic disc coloboma can be associated with coloboma, heart defects, atresia of choanae, mental retardation, genitourinary abnormalities and ear anomalies (CHARGE association).

f) Morning glory syndrome (MGS) is an optic neuropathy characterized by a congenital funnel shaped excavation of the posterior fundus that incorporates the optic disc

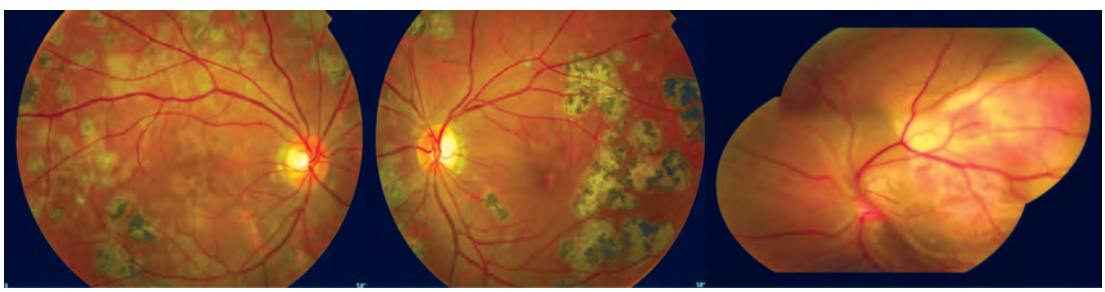

Fig.5a. Bilateral TB multifocal choriditis **Fig.5b. Choroidal granuloma**

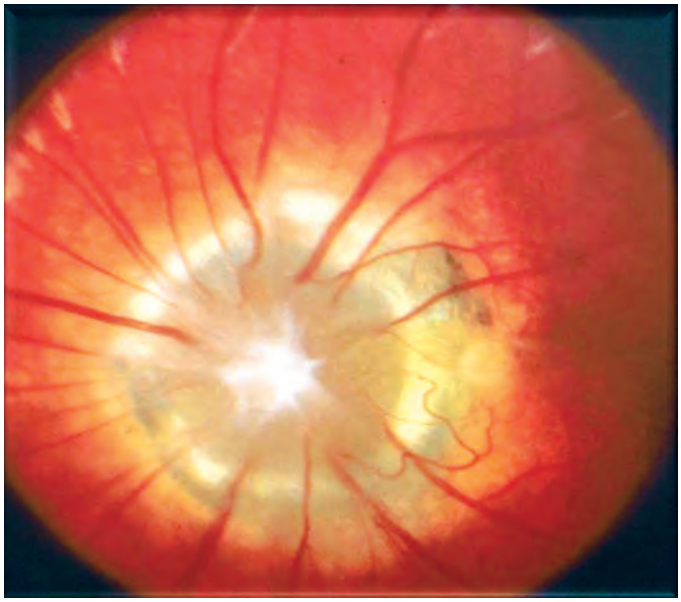

Fig.7. Morning glory optic disc anomaly

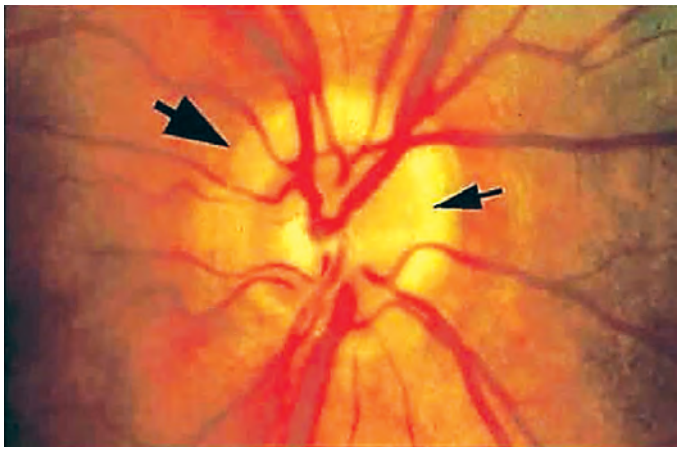

Fig.8. Small optic disc with a double ring sign in optic nerve hypoplsia

malformation (resembling the morning glory flower) as seen in Fig.7. It can be associated with midline cranial defects like trans-sphenoidal encephalocele with or without corpus callosal agenesis and dysmorphic features, including a wide head, flat nose, hypertelorism and a midline notch in the upper lip. Another rare association is abnormal carotid circulation, such as carotid stenosis/aplasia or progressive vascular obstruction with collateralization (also known as Moya Moya). It is a rare, progressive cerebrovascular disorder caused by blocked arteries at the base of the brain in the basal ganglia. The name "Moya Moya" means "puff of smoke" in Japanese and describes the look of the tangle of tiny vessels formed to compensate for the blockage. These vascular defects may lead to ischemia, stroke or seizures and so a finding of morning glory disc should lead to further diagnostic radiographic imaging.

g) Optic nerve hypoplasia (ONH) is the underdevelopment of the optic nerve(s).[8] It is the most common congenital optic nerve anomaly. The optic disc appears abnormally small often with a double ring sign as seen in Fig.8 and is often associated with endocrinopathies (hormone deficiencies), developmental delay and brain malformations. De Morsier's Syndrome or septo-optic dysplasia (SOD) is associated with ONH. It can involve multiple problems in the midline structures of the brain, stemming from miswiring of the brain and central nervous system. There can be agenesis of the corpus callosum, absence of the septum pellucidum, maldevelopment of the anterior and posterior pituitary gland and anomalies of the hypothalamus. Due to the above-mentioned associations, all children with ONH are at risk for developmental delays and hormonal deficiencies, regardless of severity of ONH, or whether abnormalities are visible by MRI. Some of the risk factors include maternal insulin dependent diabetes mellitus (IDDM), maternal ingestion of anticonvulsants, alcohol, maternal infections like CMV, Hepatitis B, low parity and young maternal age. Detection of ONH by a retinal examination can help prevent morbidity and mortality by endocrine screening in infants.

h) Other miscellaneous optic nerve anomalies can be waxy pale disc in retinitis pigmentosa, optic nerve head drusen (small yellowish deposits of cellular debris that accumulate under the retina) and myelinated nerve fiber.[8]

In conclusion, retinal examination of children and infants is an essential part of a pediatrician's examination and will lead to a great reduction in the incidence of preventable blindness by timely referral of the affected children.

Points to Remember

- ***Visual assessment and fundus examination in children can be a guide to systemic diseases.***
- ***Direct and indirect ophthalmoscopy are diagnostic equipment for retinal examination.***
- ***RetCam is a very important telemedicine tool for retinal examination of preterm babies to detect retinopathy of prematurity.***
- ***Role of pediatricians in eye care is very important as they are the primary treating physicians who are in contact with the children.***

- ***Early referral to an ophthalmologist can reduce the incidence of childhood blindness.***

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CLIPPINGS

Effectiveness of SARS-CoV-2 decontamination and containment in a Covid-19 ICU

Health care systems in the United States are continuously expanding and contracting spaces to treat patients with coronavirus disease 2019 (COVID-19) in intensive care units (ICUs). As a result, hospitals must effectively decontaminate and contain severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in constructed and deconstructed ICUs that care for patients with COVID-19. We assessed decontamination of a COVID-19 ICU and examined the containment efficacy of combined contact and droplet precautions in creating and maintaining a SARS-CoV-2-negative ICU "antechamber". To examine the efficacy of chemical decontamination, the investigators used high-density, semi-quantitative environmental sampling to detect SARS-CoV-2 on surfaces in a COVID-19 ICU and COVID-19 ICU antechamber. Quantitative real-time polymerase chain reaction was used to measure viral RNA on surfaces. Viral location mapping revealed the distribution of viral RNA in the COVID-19 ICU and COVID-19 ICU antechamber. Results were further assessed using loop-mediated isothermal amplification. Results: We collected 224 surface samples pre-decontamination and 193 samples post-decontamination from a COVID-19 ICU and adjoining COVID-19 ICU antechamber. We found that 46% of antechamber objects were positive for SARS-CoV-2 pre-decontamination despite the construction of a swinging door barrier system, implementation of contact precautions, and installation of high-efficiency particulate air filters. The object positivity rate reduced to 32.1% and viral particle rate reduced by 95.4% following decontamination. Matched items had an average of 432.2 ± 2729 viral copies/cm2 pre-decontamination and 19.2 ± 118 viral copies/cm^2 post-decontamination, demonstrating significantly reduced viral surface distribution ($p < 0.0001$). Environmental sampling is an effective method for evaluating decontamination protocols and validating measures used to contain SARS-CoV-2 viral particles. While chemical decontamination effectively removes detectable viral RNA from surfaces, our approach to droplet/contact containment with an antechamber was not highly effective. These data suggest that hospitals should plan for the potential of aerosolized virions when creating strategies to contain SARS-CoV-2.

Brune Z, Kuschner CE, Mootz J, Davidson KW, Pena RCF, Ghanem MH, et al. Effectiveness of sars-cov-2 decontamination and containment in a Covid-19 ICU. Int J Environ Res Public Health_2021 Mar 3; 18(5):2479.doi: 10.3390/ijerph18052479.

IAP - IJPP CME 2021

AUTOIMMUNE ENCEPHALITIS - A REVIEW

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****Sheffali Gulati**

Abstract: *Autoimmune encephalitis is a group of immune mediated diseases, with inflammation of the central nervous system that demonstrates a widely variable spectrum of clinical presentations. It is caused by binding of antibodies to the intracellular/cell-surface antigens, producing typical syndromes. Anti-N-methyl-D-aspartate receptor encephalitis is the most common form in children and the clinical presentation differs from that of adults. Children present with alteration in consciousness, seizures, movement disorders, behavioral and sleep disturbances. Investigations, especially antibody detection, along with suggestive history aids in the diagnosis. Treatment is based on immunotherapy and early initiation of therapy is associated with better outcome.*

Keywords: *Anti-NMDAR encephalitis, Children, Movement disorders, Immunomodulation.*

Encephalitis in children is associated with significant morbidity and mortality, all over the world. Of the various etiologies identified, infectious etiology forms the major chunk.[1] However, autoimmune encephalitis (AIE) is rapidly gaining recognition as an important cause of encephalopathy in children, which is treatable. AIE in children remains a diagnostic challenge because of its similarity in clinical presentation with other diseases, especially those associated with inflammation or immune mediated damage of the central nervous system.[2] Despite a multitude of antibodies being attributed to autoimmune encephalitis, anti-NMDAR (anti-N-methyl-D aspartate receptor) encephalitis remains the most frequently encountered cause in children, while a majority of childhood autoimmune encephalitis do not show the presence of any known antibodies, posing a tough challenge for the clinicians.[3] Anti-NMDAR and ADEM (acute disseminated encephalo-myelitis) constitute the two most common forms of AIE described in children, whose disease course, response to therapy, functional recovery and long-term neuropsychological outcomes have been studied well over the past few years.[4,5] AIE in the pediatric age group usually manifests with acute or sub-acute onset neuropsychiatric symptoms, resulting from an abnormal immunological response in the brain.

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Epidemiology

The prevalence of autoimmune encephalitides as a group are more frequent than individual viral etiologies, but the exact prevalence of each of these disorders is not well known. The California encephalitis project, carried out between 1997-2010, initially revealed that in around 63% patients, the etiology remained unproven, after testing for 16 pathogens. Later, in the same study, it was proven that the frequency of anti-NMDA positivity surpassed that of any viral encephalitis. Similarly, a multicentric study in UK, showed that at least 4% of encephalitis patients were positive for anti-NMDA antibodies, making it one of the leading causes of acute encephalitis in children.[6] A retrospective analysis of data gathered over a period of seven years from Hong Kong, estimated an incidence of 2.2 per million children to be developing anti-NMDAR encephalitis every year, accounting for a large proportion of cases with encephalitis in children.[7] However, limited data is available regarding pediatric AIE.

At our centre, between Jan-2014 to Aug-2017, a total of 544 children presented with acute-onset, non-traumatic encephalopathy. The settings in which AIE was suspected were - (a) recognizable clinical syndromes of antibody positive encephalitis or limbic encephalitis, (b) evidence of inflammation on MRI brain or cerebrospinal fluid (CSF), (c) presence of other autoimmune diseases, or (d) good response to immunotherapy. Based on this, 51 children were diagnosed as AIE (40 were definite AIE - antibody positive and 11 were probable AIE - seronegative).[8]

Table I. Intra-cellular and cell-surface antigen based diseases

Intra-cellular antigen based	Cell-surface antigen based
Strong association with malignancy (Para-neoplastic)	May or may not be associated with malignancy
Mediated by cytotoxic T cells	Mediated by B cell response
Poor response to immunomodulatory therapy	Better response to immunomodulatory therapy
Poor outcome	More favourable outcome

Etio-pathogenesis

Several antibodies have been implicated in the pathogenesis of autoimmune encephalitis. Pediatric AIE have been categorised into two groups based on the antigen location against which the antibodies are directed - intra-cellular antigens and cell-surface antigens. The two groups differ not only on the antigen location but also in their clinical features (Table I).[9,10]

Frequency of antibody positivity in AIE in two different studies is shown in Table II. In the study by Gulati S et al., in (anti-NMDAR) positive AIE the pathogenicity is due to IgG1 antibodies which are directed against the GluN1 subunit of N-Methyl-D-aspartic acid receptor leading to its internalization.[8]

Various etiopathogenetic mechanisms have been proposed, of which para-neoplastic processes are more pronounced in adults. However, para-neoplastic syndromes have lesser clinical relevance in pediatric AIE, as compared to infections and vaccines. In post-viral AIE, the release of brain-specific antigens due to viral toxicity, triggers the development of pathogenic auto-antibodies. Pruss, et al had reported anti-NMDAR positivity in 30% of patients with HSV encephalitis and 20% of the cases with relapsing symptoms following HSV encephalitis, was attributable to anti-NMDAR antibodies, with a higher frequency noted in children.[12] These relapses show significant response to immunomodulatory therapy. Other viral infections like Varicella Zoster virus (VZV), Epstein Barr virus (EBV), cytomegalovirus (CMV), adenovirus, human immune-deficiency virus (HIV) and rickettsial infection, have also been reported to predate AIE, albeit much less common than HSV. Apart from anti-NMDAR antibodies, other antibodies like anti-D2 receptors, anti-GABA-A/B receptors and anti-á-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antibodies have also been detected in post-viral AIE. Other than infections, many cases of anti-NMDAR encephalitis have been described following vaccination of children with DPT (Diphtheria, Pertussis, Tetanus), polio, influenza (H1N1) and Japanese B encephalitis.[13]

Table II. Antibody positivity in AIE[8,11]

Study groups	Study population	Antibody positive
de Bruijn, et al[11]	113 patients fulfilled the criteria for possible AIE	*21 patients* anti- NMDAR: 19 anti-AMPAR:1 anti-LGI1: 1 anti-TPO:2 ADEM: 34
Gulati S, et al[8]	51 children diagnosed with AIE	*40 children* anti-NMDAR: 24 anti-basal ganglia:7 anti-GAD:3 anti-MA:2 anti-TPO:2 anti-YO:1 anti-CRMP5:1

NMDR: N-methyl D-aspartate receptors, AMPAR: á-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, anti-LGI1: Anti leucine-rich glioma inactivated 1, CRMP 5 - collapsin response mediator protein 5, GAD: glutamic acid decarboxylase, anti-TPO: Anti-thyroid peroxidase, ADEM: Acute disseminated encephalomyelitis

Table III. Encephalitis - Diagnostic criteria

Major criteria (Necessary)
Altered mental status (decreased or altered level of consciousness, lethargy or change in personality from baseline) lasting for more than 24 hours, with no other alternative etiology identified
Minor Criteria*
Fever ≥ 38°C (100°F) within 72 hours before or after the presentation
Generalised or focal seizures (Not attributable to pre-existing seizure disorder)
New onset focal neurological findings
Leukocyte count ≥ 5/mm^3 in CSF
Neuroimaging suggestive of abnormality in the brain parenchyma, which is either of acute onset or new from the lesions of previous imaging studies
EEG findings suggestive of encephalitis and not attributable to another cause

**Presence of Major criterion along with 2 minor criteria suggests a possible encephalitis, while the presence of ≥ 3 minor criteria suggest a probable or confirmed encephalitis.*

Table IV. Clinical features of AIE in children and adults

Children	**Adults**
Usually, post-infective	Can be post-infective, but usually associated with tumours
Tachycardia, hypertension, hyperthermia	Arrhythmia, hypoventilation
Seizures, movement disorders, speech abnormalities and sleep disturbances	Psychosis and behavioral disturbances

Definitions and diagnostic criteria

Previous studies showed that specific etiologies were identifiable in < 50% cases, partly due to lack of consensus on definitions and partly to lack of standardised diagnostic approaches. In 2013, the International Encephalitis Consortium, proposed the diagnostic criteria for encephalitis (Table III).[1]

The drawback of this criteria was its inability to differentiate between encephalitis of infectious and autoimmune etiology. Hence, there was a necessity to define the diagnostic criteria for autoimmune encephalitis. In 2016, Graus, et al developed diagnostic criteria for early diagnosis of AIE in adults. Criteria was also set for the diagnosis of specific neurologic syndromes, like anti-NMDAR encephalitis, seronegative encephalitis and limbic encephalitis.[14]

However, there are differences between the presentation of AIE in adults and children (Table IV). Fever occurring as a prodrome, is noted in more than 50% of the patients.[5] Altered level of consciousness, behavioral disturbances, movement disorders, seizures and sleep disturbances are the common neurological manifestations in these children. Seizures are a common presenting complaint in children with AIE and may be generalised, focal or multifocal. More than 30% of the children present with movement disorders - choreo-athetoid movements, dystonia, myoclonus, tremors and ataxia.[3,4] Developmental regression with loss of language milestones and speech impairment are common presenting features in pediatric AIE. Stereotypies, aggression, excessive irritability, hyperactivity, insomnia and other behavioral changes are quite common in children with AIE.[3,4] Psychiatric manifestations like personality changes and fulminant psychosis, are less common in children as compared to adults. However, the presence of such features in children ≤ 12 years, should prompt one towards an underlying medical condition, than an obvious psychiatric condition.[3,4] The pathophysiologic mechanism in children with AIE differs from that of adults due to the evolution of neuronal circuitry, receptor densities and myelination during the normal development.[15]

Hence, there was a need for modification of the criteria, to be applicable in children. Recently, a subcommittee of the Autoimmune Encephalitis International Working Group, refined the existing consensus criteria for AIE in adults, for its use in children, which is based on clinical history relevant in pediatric AIE and supportive diagnostic tests (Table V).[15]

Clinical features

AIE in children has a varied presentation which includes fever, seizures, movement disorders, altered state of consciousness, neuropsychiatric manifestations and memory disturbances. Certain features favouring and pointing against pediatric autoimmune encephalitis have been given in Table VI.

Table V. Pediatric AIE - Classification

Features of AIE	Possible AIE	Probable (Ab negative AIE)	Definite (Ab positive AIE)
Evidence of acute or subacute symptom onset[a]	Yes	Yes	Yes
Clinical evidence of neurologic dysfunction[b]	≥2 features	≥2 features	≥2 features
Paraclinical evidence of neuro inflammation[c]	Not done	≥1 feature	≥1 feature
AIE serology[d]	Not done	Negative	Positive
Exclusion of other etiologies[e]	Yes	Yes	Yes

a) Onset of neurologic and/or psychiatric symptoms over ≥ 3 months in a previously healthy child

b) Altered level of consciousness, EEG with slowing or epileptiform activity, focal neurologic deficits, cognitive difficulties, acute developmental regression, movement disorder (except tics), psychiatric symptoms, unexplained seizures

c) CSF inflammatory changes (Leukocytes >5 cells/mm^3, oligoclonal bands), MRI features of encephalitis, brain biopsy showing inflammatory infiltrates, excluding other disorders

d) Presence in serum and/or CSF of well characterized autoantibodies associated with AIE

e) Reasonable exclusion of alternative causes, including other causes of CNS inflammation

Table VI. Pointers for and against pediatric AIE

Favourable points	Features suggesting alternative diagnosis
• Acute onset and rapidly progressive decline in consciousness	• Chronic indolent course
• Cognitive impairment	• Stabilizing of symptoms
• Recurrent seizures (drug refractory or status epilepticus)	• Pure psychiatric manifestations
• Autonomic instability	• Preserved cognition with no impairment in activities of daily living
• Urinary/fecal incontinence	
• Relapse after treatment for viral encephalitis	
• Movement disorders	

Among the various AIE in children, the most common form, anti-NMDAR encephalitis, presents in three phases. It usually manifests with fever in the prodromal first phase. In the second phase, neurological manifestations develop in the form of altered state of consciousness, psychosis (delusions, hallucinations, catatonia), seizures, memory impairment and speech disturbances. In the final third phase, the children develop movement disorders, autonomic instability and occasionally hypoventilation.

Choreo-athetoid movements and peri-oral dyskinesias are the characteristic features of these children. These movements sometimes occur early in the disease and are progressive in nature, thus, directing us towards the diagnosis. Anti-NMDAR encephalitis has been described to have three clinical phenotypes - the a) classic and b) the psychiatric forms which have a good outcome and c) the catatonia predominant form which has a poor outcome.[16]

Each of the various pediatric autoimmune encephalitis syndromes, based on the associated antibody, have certain characteristic features and given in Table VII.

Diagnostic evaluation

Various ancillary investigations aid in the diagnosis of AIE in the presence of appropriate clinical features. All other possible common differentials should be ruled

Table VII. Characteristic features of various antibodies associated with AIE

Intra-cellular antigens		Cell - surface antigens	
Antibody	**Clinical features**	**Antibody**	**Clinical features**
AGNA (SOX1)	LE, neuropathy	**NMDAR**	NMDAR encephalitis
Amphiphysin	LE, neuropathy, myelopathy, cerebellar degeneration stiff person syndrome OMA	**AMPAR**	LE, Pure psychiatric symptoms
ANNA-1 (anti-Hu)	LE, cerebellar degeneration, neuropathy, encephalomyelitis, OMA	**$GABA_AR$**	Status epilepticus, stiff person syndrome
ANNA-2 (anti-Ri)	OMA, brainstem encephalitis	**$GABA_BR$**	LE, status epilepticus
ANNA-3	Cerebellar degeneration, encephalomyelitis	**LGI-1**	LE, faciobrachial dystonic seizures
CRMP-5	LE, cerebellar degeneration **(anti-CV2)**	**CASPR2**	Encephalitis, Morvan syndrome
GFAP	Encephalitis, meningoencephalitis, myelitis, neuropathy, meningitis	**GlyRáR**	PERM, LE, stiff person syndrome, cerebellar degeneration
Anti-Ma	Cerebellar and brainstem dysfunction LE Brainstem encephalitis	**mGluR1**	Cerebellar degeneration
PCA-1	Cerebellar syndrome, neuropathy	**mGluR5**	Ophelia syndrome Hodgkin's lymphoma
PCA-2	LEMS, cerebellar degeneration, encephalomyelitis	**DPPX**	Encephalitis, psychiatric, PERM Diarrhea Profound weight loss
ZIC	Encephalomyelitis, cerebellar degeneration, OMA	**Neurexin-3α**	Encephalitis, seizures
GAD-65	Encephalitis, stiff person syndrome, cerebellar ataxia, seizures, encephalomyelitis, OMA	**PCA-Tr (anti-DNER)**	LE, cerebellar degeneration
		VGCC	Encephalopathy, seizures, cerebellar degeneration, LEMS
		IgLON5	Ataxia, chorea, sleep disorders

LE: Limbic encephalitis, LEMS: Lambert-Eaton myasthenic syndrome, OMA: Opsoclonus-Myoclonus Ataxia, PERM: Progressive encephalomyelitis with rigidity and myoclonus, ANNA-1:type 1 antineuronal nuclear antibodies, ANNA-2: type 2 antineuronal nuclear antibodies, ANNA-3: type 3 antineuronal nuclear antibodies, CRMP-5:collapsin response mediator protein 5, GFAP: Glial fibrillary acidic protein, GlyRáR: Glycin Receptor α 1, mGluR1: metabotropic glutamate receptor 1, mGluR5metabotropic glutamate receptor 5, DPPX: Dipeptidyl-Peptidase–Like Protein-6, ZIC: zinc-finger protein of the cerebellum , GAD-65: glutamic acid decarboxylase, anti-DNER: anti-delta/notch-like epidermal growth factor-related receptor, VGCC: Voltage gated calcium channel, AGNA: Antiglial nuclear antibody, AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, LGI-1:Leucine-rich, glioma inactivated 1, CASPR2: Contactin-associated protein-like 2, PCA-Tr: Purkinje cell cytoplasmic antibody type 2, mGluR5: metabotropic glutamate receptor 5

Table VIII. AIE mimics in children

Primary CNS inflammatory disorders
Primary or secondary CNS vasculitis
Demyelinating diseases: Neuromyelitis optica spectrum disorders (NMOSD), myelin oligodendrocyte associated disorders (MOG), pediatric multiple sclerosis
Rasmussen encephalitis
Systemic inflammatory disorders
Autoimmune diseases: Anti-phospholipid syndrome (APS), Behcet disease, sarcoidosis, systemic lupus erythematous (SLE), Sjogren syndrome
Autoinflammatory: Hemophagocytic lymphohistiocytosis (HLH)
Bacterial: Lyme's disease, listeria, mycoplasma, tuberculosis, neurosyphilis
Viruses: HSV, HIV, rabies, enteroviruses, adenovirus
Postinfectious: Post-mycoplasma basal ganglia encephalitis, Post HSV NMDA encephalitis, encephalitis lethargica
Diseases with immune mechanism under review
Febrile infection related epilepsy syndrome (FIRES)
Acute necrotizing encephalopathy of childhood (ANEC)
Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)
Pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections (PANDAS)
Pediatric acute-onset neuropsychiatric syndrome (PANS)

out apart from confirming AIE with antibody testing. The list of differentials that closely mimic AIE in children is given in Table VIII.

Antibody testing: Routine CSF examination is usually normal, while a few patients may show lymphocytic pleocytosis (<100 WBCs/μl) with elevated protein levels (<100 mg/dL). CSF and serum are tested for the various possible IgG antibodies, wherever possible. Live or fixed cell-based assays (CBA) are used for testing of these antibodies. They bind to the extra-cellular epitopes of proteins on the cell surface like ion channels, synaptic proteins and receptors, whose conformation and shape determine the antibody binding.[17] Apart from anti-NMDA encephalitis, where CSF is found to be more sensitive than serum (100% vs 85.6 %)[4] for detection of antibodies, all other antibodies are detected with almost similar sensitivity in both CSF and serum. Hence, in resource constraint settings, CSF is the preferred sample for antibody testing, especially in anti-NMDAR encephalitis. The follow up evaluation of these antibodies is not recommended as of now, as their utility in follow up has not yet been ascertained. The antibodies tend to persist in the CSF, in those whose who have a protracted clinical course and those who have received IV immunoglobulin or undergone plasmapheresis. Oligoclonal bands (OCBs) are detected in the later stage of the illness.

MRI brain: Most of the patients (66%) with anti-NMDAR encephalitis do not exhibit any abnormalities on neuroimaging. In contrast, most of the patients with anti leucine-rich glioma-inactivated 1 (anti-LGI 1) antibodies, have mesial temporal hyperintensities, which progresses to mesial temporal sclerosis on follow up. Unilateral or bilateral T2/FLAIR signal hyperintensities involving the mesial temporal lobes, are the classical MRI abnormalities seen in children with AIE. Positron emission tomography (PET) in patients with normal MRI, but strong clinical suspicion and corroborating EEG findings, may reveal involvement of the mesial temporal lobes. In some cases, rarely diffuse involvement of the entire brain may also be seen. In children with anti-GABA-A receptor encephalitis, MRI brain is abnormal with extensive multifocal or diffuse signal alterations, while those with anti-D2 receptor encephalitis show involvement of the bilateral basal ganglia. These MRI findings are neither sensitive nor specific to these disorders, however, in appropriate clinical setting they may aid in the diagnosis.

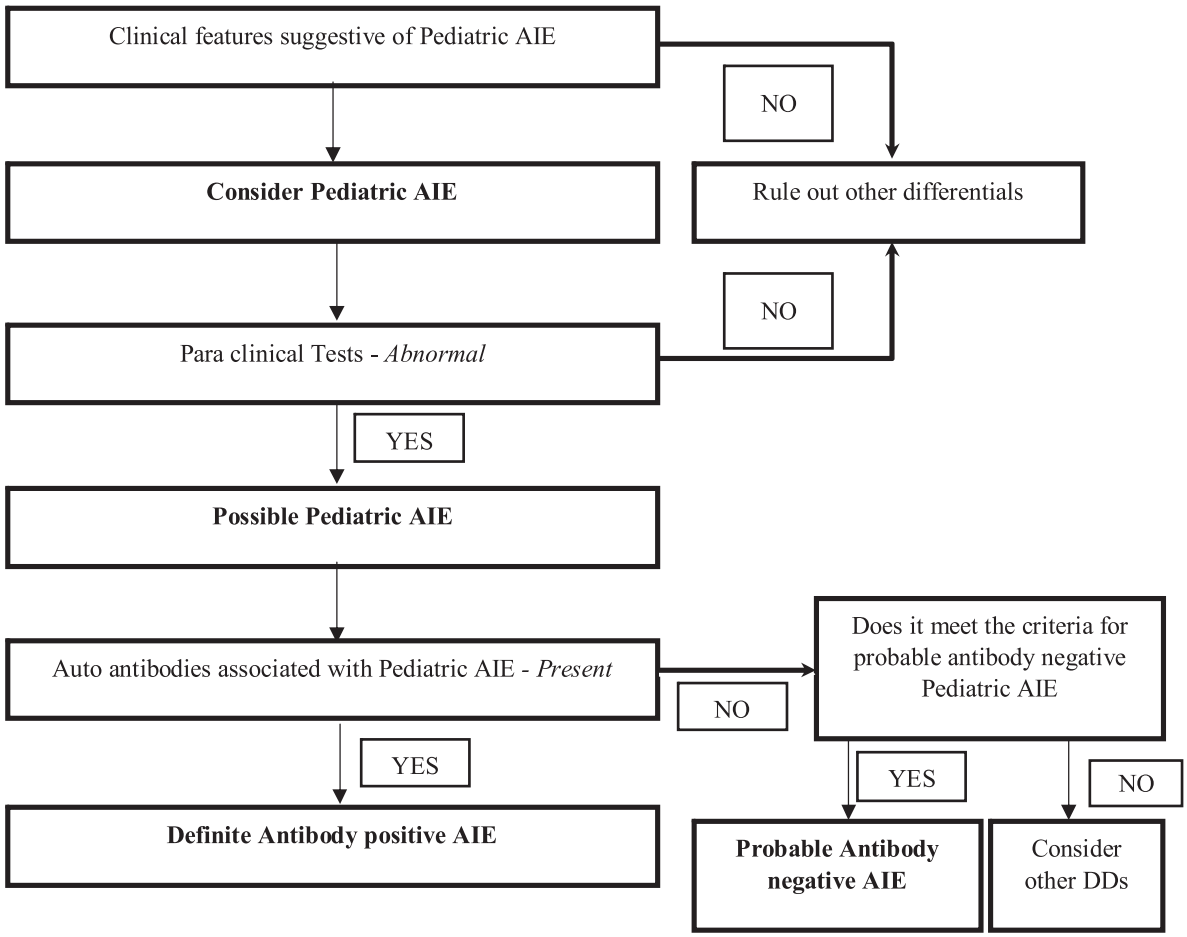

Fig.1. AIE in children - Diagnostic algorithm (Based on the autoimmune encephalitis international working group guidelines)[15]

Electroencephalography (EEG): A typical 'delta-brush' pattern in seen in around 30% of children with anti-NMDAR encephalitis. However, in most patients of pediatric AIE, the EEG may show non-specific findings in the form of diffuse (occasionally focal) slowing along with epileptiform discharges. In most of the children, the EEG may not be contributory to the diagnosis. EEG is mainly performed to rule out non-convulsive status epilepticus (NCSE) in these children.

In children of adolescent age group, especially females, screening for malignancy like ovarian teratomas also needs to be undertaken (chest, abdomen and pelvic imaging). Fig.1 elucidates the diagnostic algorithm for AIE in children.[15]

Treatment

Early initiation of immunomodulatory therapy is associated with better prognosis. On suspicion of AIE, empirical therapy is indicated, instead of waiting for the results of antibody testing. Children receiving immunotherapy for autoimmune encephalitis fare better than those not given immunotherapy. No clinical trials have studied the optimal therapeutic regimen in management of pediatric AIE. The primary options available are corticosteroids, intravenous immunoglobulins (IVIG) or plasmapheresis (PLEX), for acute management. Acute management is followed by maintenance therapy, which is given in the form of oral steroid taper, monthly pulse steroids or monthly IVIG doses. Maintenance therapy is given for a total duration of 6 to 12 months. Steroid sparing agents like azathioprine and mycophenolate mofetil are also used for maintenance therapy. Other second line agents like rituximab, cyclophosphamide and third line agents like tocilizumab and bortezomib are used in non-responders and in those with relapse. Relapses occur infrequently in children with AIE and are managed with repeat dosing of 1st line agents. However, a long-term immunomodulation using steroid sparing agents, is generally given in those who have a relapse. In case of associated tumors, simultaneous oncological treatment is essential for holistic management.

Corticosteroids: In view of good penetrability across the blood-brain barrier and wide spectrum of immunomodulatory activity, corticosteroids have been the mainstay of therapy. Intravenous pulse methylprednisolone (30 mg/kg/day, max -1 g/day) is given for 3 to 5 days, followed by oral steroids (prednisolone 1-2 mg/kg/day, max- 60 mg/day). The oral steroids are tapered over 6 to 12 months. Adverse effects of long term steroid usage must be taken care of, like cataract, hypertension, weight gain, etc.

Intravenous immunoglobulin (IVIG) and plasmapheresis: These are often used as alternatives to steroids, but are also used simultaneously, occasionally. A systematic review of 71 articles (n = 242) by Suppiej, et al, showed that use of corticosteroids with early PLEX, had better outcome than those who received either steroids or PLEX, in children with anti-NMDAR encephalitis.[18] PLEX is performed by 5 to 7 exchanges of 50 ml/kg every alternate day, while IVIG (2 g/kg) is administered over 5 days. In view of agitated state of children, due to practical ease, IVIG is preferred over PLEX. However, no study has yet proven the superiority between the two. A significant proportion of pediatric AIE cases show response to 1st line agents, within first 2 weeks of treatment initiation.

Maintenance therapy: Steroid-sparing agents like azathioprine, mycophenolate mofetil (MMF) and occasionally, methotrexate have been used in pediatric AIE, for maintenance therapy.[19] A systematic review of retrospective data, showed decreased risk of relapse, if these agents are added to the regimen after the initial event rather than subsequent ones. There has been no consensus regarding the total duration of maintenance therapy, but it is usually given for 9 to 12 months.

Second and third line agents: While most of the patients respond to 1st line agents, a few either do not respond or show inadequate response. These patients are treated with second line (rituximab, cyclophosphamide) and third line agents (tocilizumab, bortezomib). Among them, rituximab is the most used agent, an anti-CD20 chimeric monoclonal antibody, causes B-cell depletion, leading to decreased pro-inflammatory responses.

Symptomatic treatment: Apart from immunomodulatory therapy, symptomatic therapy also forms an important aspect of management. Anti-seizure medications for seizures, benzodiazepines and sedatives for sleep disturbances and agitated state, are frequently required in these children.

Case Vignettes

A few example cases illustrate the clinical presentations of the common pediatric autoimmune encephalitis syndromes.

Case vignette 1: A 10-year-old girl, developmentally normal, presented with acute onset changes in personality and behavioral disturbances - aggressiveness, emotional lability for 2 weeks, with involuntary choreoathetoid movements and a single episode of GTCS. On examination, she was drowsy, not oriented to time and place, could recognize parents, follow simple commands, with slurred speech with choreoathetoid movements and orofacial dyskinesias. MRI brain and routine CSF analysis were normal. EEG showed a generalized diffuse slowing with frequent epileptiform discharges. CSF and serum for infectious etiology were negative. However, both serum and CSF were strongly positive for anti-NMDAR antibodies. A final diagnosis of anti-NMDAR encephalitis was made. Screening for any occult malignancy was done,which was negative. She showed significant improvement in her symptoms within 1 week of initiation of immunotherapy.

Case vignette 2: A 15-year-old premorbidly normal boy, presented with headache, psychiatric abnormalities-abusive, aggressiveness for 1 week and was brought convulsing to casualty, which progressed to refractory status epilepticus. After 12 hours, despite the cessation of seizures, there was no improvement in the child's sensorium. Initial metabolic screen and CT brain (with contrast) were normal. CSF examination didn't reveal any abnormality. EEG done was suggestive of non-convulsive status epilepticus. Hiking of anti-seizure medications led to gradual improvement in the sensorium. MRI brain done after stabilization of the child showed T2/FLAIR hyperintensities in the left hippocampus and the mesial temporal lobe. CSF for HSV DNA PCR as well as autoimmune antibodies panel was negative. He was treated with immunotherapy as a case of seronegative autoimmune encephalitis (Limbic encephalitis).

Case vignette 3: A 10-month-boy was brought to the casualty with fever, excessive irritability, poor feeding and altered sleep wake cycles for last 3 days. On examination, the child also had ballismus and chore-athetoid movements of all the limbs. Four weeks prior to this, child had fever, seizures (GTCS), abnormal involuntary movements, with sleep disturbances. CSF done at that time had shown lymphocytic pleocytosis (cells - 20/ mm^3) (97% lymphocytes), with normal sugar (51 mg/dL) and protein (47 mg/dL). He received acyclovir empirically for

14 days, though CSF for HSV DNA PCR was negative. Following this the child had improved, however, now he was brought with the above complaints. A repeat CSF analysis was strongly positive for anti-NMDAR antibodies. Hence, the child was diagnosed with post-HSE (herpes simplex encephalitis) anti-NMDAR encephalitis. He received IVIG and PLEX (5 cycles) following which there was marked improvement in choreoathetosis and dyskinesias in 3 days and subsequently the child is on improving trend.

Prognosis

AIE in children with antibodies directed against intracellular antigens have a poor prognosis, while those directed against cell surface antigens have a good prognosis. Titulaer, et al found that 94% of children with anti-NMDAR encephalitis responded within four weeks of initiation of steroid therapy.[4] At 2-year follow up, 81% had good outcome with 6% mortality. Around 12% of these children have a relapse, which requires 2nd and 3rd line agents. Early initiation of therapy and lack of admission into critical care unit are predictors of good outcome. A systematic review by Broadley, et al, showed that delay in initiating immunotherapy led to worser outcomes in subsets of patients with autoimmune encephalitis.[20]

Conclusion

AIE is a difficult disease to diagnose and treat. Early identification of AIE based on clinical and serological clues can guide definite immunotherapy. Early initiation of treatment is associated with better long-term outcomes in pediatric AIE. An escalating algorithm of immunotherapy modulated to the clinical response of the patient may be rewarding in the setting of suspected AIE.

Points to Remember

- ***AIE in children as a group is more common than individual viral etiologies of encephalitis in children.***
- ***Anti-NMDAR encephalitis is the most common autoimmune encephalitis in children.***
- ***AIE in children is commonly post-infectious in etiology and is less commonly associated with malignancy, unlike in adults.***
- ***Characteristic clinical features include seizures, movement disorders (peri-oral dyskinesias, choreoathetoid movements), behavioral issues and sleep disturbances.***
- ***The antibodies are detected with almost equal sensitivity in both serum and CSF, except in anti-NMDA encephalitis, where the sensitivity in CSF is marginally better.***
- ***Treatment options include steroids, IVIG, plasmapheresis and in refractory cases, rituximab and cyclophosphamide.***
- ***Early initiation of immunotherapy leads to a better outcome.***

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CLIPPINGS

Association between laboratory parameters and CT severity in patients infected with COVID-19: A retrospective, observational study

Patients diagnosed with COVID-19 have presented to emergency departments (EDs) worldwide with a wide range of symptoms. The study reported the clinical, laboratory and radiological features of the cases diagnosed with COVID-19. This is a single-center, retrospective, descriptive, and observational study. The patients who have admitted to ED between March 11 and May 31, 2020 and diagnosed COVID-19 infection. RESULTS: 130 (73 male and 57 female) patients with COVID-19 polymerase chain reaction (PCR) positive test were included in the study. The average age of the study group was calculated as 52.63 ± 17.95 year. While 15.4% of the patients were asymptomatic, the most common symptom was identified as cough (46.2%), followed by dyspnea (23.1%), fever (17.7%). The computed tomography (CT) severity scores proved significantly higher in the patients with hypertension and coronary artery disease (CAD) than in those without these diseases ($p = 0.010$ and $p = 0.042$, respectively). The moderate positive correlation between serum ferritin level and CT severity score is another finding worth noting (rho = 0.530 and $p = 0.0001$). In a similar vein, the high level of D-dimer in the CT-positive group and its positive moderate correlation with CT severity (rho = 0.375 and $p = 0.0001$). In our study, serum ferritin and D-dimer levels were observed to be high in the CT-positive group and have moderate positive correlation with CT severity. D-dimer and ferritin levels measured at the time of admission to the ED can be taken into consideration to predict radiological severity.

Yilmaz A, Sabirli R, Seyit M, Ozen M, Oskay A, Cakmak V, et al. Association between laboratory parameters and CT severity in patients infected with Covid-19: A retrospective, observational study. Am J Emerg Med. 2021 Apr; 42: 110-114.Published online 2021 Jan 20. doi: 10.1016/j.ajem.2021.01.040.

IAP - IJPP CME 2021

COUNSELING IN DIFFICULT SITUATIONS

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****Rohit Vohra**

Abstract: *Pediatric intensive care unit practice has remarkably changed in recent years. These units have experienced transformation in care and humanization of assistance, providing access round the clock. In the current era, the pediatric intensivist plays the role of a healthcare provider and a counsellor who apprises the family members of the prognosis of the disease to allay anxiety about the child's condition.Thus, pediatric intensive care unit-doctor must be an expert in parental counseling. Communication skills, empathy and honesty are attributes that the physician should employ during difficult situations.*

Keywords: *Critically ill child, Intensive care, Counseling, Anxiety, Stress.*

Pediatric intensive care units (PICUs) have increasingly become complex in recent decades. Clinical outcomes have improved remarkably due to monitoring systems and technological advances in the diagnosis and treatment of various diseases. Nowadays, most PICUs promote 24-hours access, with clear benefits to children, families and professionals. In the current era, the role of the PICU physician goes beyond taking care of a sick child, it encompasses explaining to the family member about their disease condition, prognosis, morbidity, thereby alleviating parental anxiety and stress about their child's condition.

Need for counselling

Counseling is defined as the provision of professional assistance and guidance based on skills of communication and building a relationship. For most parents, especially young parents, PICU is a highly stressful environment. The very thought of admission of one's child to a PICU is scary and may instill fear in parents that their child could die or become severely disabled.[1] The environment of PICU is busy and frightening and is often dominated by sick children, bright lights, medical personnel, advanced medical equipment and shrill monitors. Usually, parents initially experience extreme levels of anxiety that approach near-alarming levels, followed by a gradual decrease of anxiety in the following days.[2] Main cause of stress for parents in the PICU is the alteration/loss of the parental role, including physical separation, limited opportunities to care for the child and no longer being the independent, primary decision-maker in charge of the child's care.[3] Parents are forced to make the transition from parents of a healthy playful child to parents of an acutely ill child. This can be an exceedingly demanding process. Parental stress can bring out various stressors like not knowing how to help their child, seeing their child frightened or in pain and not being able to be with their crying child or help their child.[4-6] Knowledge of stress allows us to plan counseling strategies for the suffering parents.

A PICU doctor along with taking care of a sick child should master the art of communication with the parents. In today's era, just ordering the right tests and prescribing the right medications is not sufficient. Counseling about disease condition is just as important. Good communication improves a parent's adjustment to illness, decreases anxiety and fear, increases adherence to treatment and results in a higher rate of satisfaction. But poor communication skills are associated with lack of understanding and incomplete adherence to the effective treatment advised and higher rates of conflict between parents and doctors/nurses. So, clinical practice is changing and much more premium is put on communication skills in these days. With the availability of internet, smartphones and other gadgets, patients nowadays have more access to medical information than before, though that information may not always be correct or complete. Besides, technological advancement have made decision-making much more complex. Patients and families need the support and advice of physicians to help interpret the information and add their clinical judgment and experience to the information they get from the worldwide web.

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In present times, dialogue between patients and physicians has become very complex and has more layers, because physicians must integrate a mountain of biomedical information with their patients' values, hopes and priorities.

Counseling tools

Communicating with parents is an art that needs to be mastered by the physician. It's not surprising that many physicians struggle as they seek to acquire this mastery. This art cannot be made perfect overnight. Patient counseling does not mean 'one-size-fits-all', as every individual has a different way of reacting to unsettling news. Thus, a physician should evolve his counseling skills and use them according to the needs of his patient's family members. A variety of communication tools and road maps can help clinicians find their way through difficult conversations.

'Not alone' is a project used by some NICUs for counseling parents. The different objectives followed by medical staff for communication with the parents are given in Box 1.[7] These objectives can be used by PICU doctors as well for counseling for parents.

Kalamazoo consensus statement

Twenty-one medical education leaders and communication experts from the United States of America and Canada developed the Kalamazoo Consensus Statement (KCS) in 1991 and then met in subsequent years to create the Kalamazoo Essential Elements Communication checklist. The Kalamazoo consensus statement group outlined key communication skills for building therapeutic relationships between clinicians and patient family members. Their goal was to delineate a set of essential elements in physician-patient communication to identify and articulate ways to facilitate teaching and assessment of communication skills at all levels of medical education.[8]

Box 1. Objectives of communication with parents in NICU

- To use the appropriate language and words
- To listen patiently family's concerns with empathy
- To decide what to say
- Not to use technical language but not to lose authoritativeness
- To complete the information given by others
- To understand if parents have understood or if they need more information
- To inform without upsetting
- Not to delude, but also not to remove hope

Kalamazoo consensus statement (KCS) has seven essential elements of communication which includes

i. Building a relationship
ii. Opening the discussion
iii. Gathering information
iv. Understanding the patient's (parents) perspective
v. Sharing information
vi. Reaching agreement on treatment plans
vii. Providing closure

Each parameter is rated from 1 to 5 on a rating scale as follows: 1: Poor 2: Fair 3: Good 4: Very Good 5: Excellent (Table I).

Counseling in special situations

As discussed earlier a physician should be adept at counseling according to his patients' needs. However, in many situations in PICU, even an experienced intensivist has to be careful. A few of these situations are described here.

1. COVID patient

Coronavirus pandemic has posed a unique challenge for the management of critical care children in PICU. Hospitalization rates of children with COVID-19 were in the range of 5.7%-20% (highest among infants) with intensive care unit admission rates in the range of 0.58% - 2%.[9] Most of the children with coronavirus disease have one or both parents with COVID-19 infection requiring quarantine or hospitalisation thus making management and counseling difficult especially in infants and toddlers. Parents of such children may become anxious about the well-being of their child and feel helpless about not being able to meet/see the child.

In such scenarios, we should use our latest and modern technologies for counseling parents through video-based telecommunication (whenever possible, through live video call). This will alleviate the parental anxiety to some extent and will increase their faith in the caregivers. The consent form can also be shared via e-mail or Whatsapp and later printouts can be taken and attached to the child's hospital records.

Table I. Parameters in Kalamazoo consensus statement

Sl.No	Parameter	Rating
1.	Builds a relationship (includes the following): • Greets and shows interest in the patient and patient's family • Uses words that show care and concern throughout the interview • Uses tone, pace, eye contact, and posture that show care and concern • Responds explicitly to patient and family statements about ideas and feelings	1- Poor 2- Fair 3- Good 4- Very good 5- Excellent
2.	Opens the discussion (includes the following): • Allows patient and family to complete opening statements without interruption • Asks "Is there anything else?" to elicit full set of concerns • Explains and/or negotiates an agenda for the visit	1- Poor 2- Fair 3- Good 4- Very good 5- Excellent
3.	Gathers information (includes the following): • Addresses patient and family statements using open-ended questions. • Clarifies details as necessary with more specific or "yes/no" questions • Summarizes and gives family opportunity to correct or add information • Transitions effectively to additional questions	1- Poor 2- Fair 3- Good 4- Very good 5- Excellent
4.	Understands the patient's and family's perspective (includes the following): • Asks about life events, circumstances, other people that might affect health • Elicits patient's and family's beliefs, concerns and expectations about illness and treatment	1- Poor 2- Fair 3- Good 4- Very good 5- Excellent
5.	Shares information (includes the following): • Assesses patient's and family's understanding of problems and desire for more information • Explains using words that family can understand • Asks if family has any questions	1- Poor 2- Fair 3- Good 4- Very good 5- Excellent
6.	Reaches agreement (If new/changed plan) (includes the following): • Includes family in choices and decisions to the extent they desire. • Checks for mutual understanding of diagnostic and/or treatment plans • Asks about acceptability of diagnostic and/or treatment plans • Identifies additional resources as appropriate	1- Poor 2- Fair 3- Good 4- Very good 5- Excellent
7.	Provides closure (includes the following): • Asks if patient and family have questions, concerns or other issues • Summarizes • Clarifies future time when progress will again be discussed • Provides appropriate contact information if interim questions arise • Acknowledges patient and family and closes interview	1- Poor 2- Fair 3- Good 4- Very good 5- Excellent

Adolescent children may express psychological distress (anxiety, sadness) by acting out differently. Some may become silent while others may feel and express anger and hyperactivity. Caregivers need to be patient with children and understand their emotions. All emotions are valid and as caregivers, we need to understand them with empathy. Help children to express disturbing feelings like anger, fear and sadness. Sometimes, engaging in creative interactive activity can facilitate this process.

A 17 year old boy was admitted in the ICU with covid pneumonia in early phase of the pandemic. He required oxygen therapy through non rebreathing mask (NRM) and regular monitoring. However, he would repeatedly get from his bed and move around the whole ICU without a face mask creating panic among other patients. Allowing him to have long video calls with his girlfriend (in those days bringing mobile phones in the ICU was strictly banned) was the only way to keep him in his bed, much to the annoyance of other patients in the ICU, the staff as well as his parents. In some situations, counseling of the child patient may be more difficult than the family.

2. Iatrogenic life-threatening complications

A. Two year-old child was shifted to PICU for hemodialysis catheter insertion in the right jugular vein. The intensivist performed the procedure after taking written consent from parents explaining to them the risk/ benefits of the procedure. After insertion of a catheter, child developed right-sided pneumothorax for which a chest tube insertion was done and the child was stabilized.

Parents counseling in such events is a difficult art to master. Parents are already disturbed due to the illness of their child and an iatrogenic event potentially further deteriorating the child's condition may cause them to become agitated. Such an event inevitably produces parents' reactions of disbelief, followed by anger and mistrust towards the physician. If parents are left alone and not counseled properly about the event and their child's condition, they will inevitably go to search for causes of what has happened. This can lead to breach of trust between the treating physician and parents and can also have medico-legal consequences.

Instead, if parents are assisted with support and honestly explained in detail as to what has happened and gently reminded that pneumothorax is a recognized complication of jugular venous cannulation which was also explained to them during obtaining consent before insertion of the catheter. The physician should emphasize the fact the child has been provided the best care (chest tube has been inserted) and he should make a complete recovery. Family members can be called to the bedside to show them the clinical condition of the child; visually seeing their child's well-being would help to relieve their anxiety and build trust in the physician. Attendants should be encouraged to ask any questions and clear all their doubts regarding the child's condition and prognosis during this counseling session.

B. Five year-old girl was being treated for acute lymphoblastic leukemia. The child developed anaphylaxis immediately after being given injection L- asparaginase in presence of the mother. The anaphylactic reaction was managed appropriately and the child stabilized. General consent for chemotherapy was taken but the prospect of anaphylaxis was not explained during the process of obtaining consent.

Parents of children with chronic illness are already troubled and witnessing one's child having an acute life-threatening event for any parent might be difficult to get over. Parents should be provided with emotional support and communicated clearly that these small setbacks can happen in treatment but they need to be strong emotionally and mentally to attend to the needs of their children.

The family member may question why the possibility of anaphylaxis was not explained to them and how could it happen when their child has already received L- asparaginase in past? To these queries, a caregiver response can be that any drug especially L-asparaginase can cause anaphylaxis. Since the risk of such a reaction happening in a child is very low, thus it was not separately explained to them earlier though consent for using such drugs had already been taken. Moreover, such a reaction can happen anytime during the treatment course and not necessarily with the first dose. It has been seen that with some drugs such reactions are more common in subsequent doses. Parents may also be worried about what effect this event will have on their treatment of their child as he requires more doses of this drug. The treating physician must console the parents that anaphylaxis will not have any effect on the long-term outcome of the disease (ALL) through severe hypersensitivity reaction to L-asparaginase means that they should not use this drug in the future. The other two alternative medicines-pegasparginase or erwinase are available which can be used.

3. Post death councelling and family guilt

Eight year-old male child was brought to ER with complaints of fever for 5 days and vomiting for 4 days. On examination, the child had meningeal signs and low

blood pressure. The child was started on antipyretics and IV fluids and advised immediate admission. However, after 1-hour fever came down and the child started feeling better so parents decided to take their child home against medical advice. On the next day, the child was again brought to ER with persistent seizures. He was admitted to PICU with hypotensive shock and required mechanical ventilation and inotropes. However, he didn't improve. In PICU parents were constantly blaming each other for not having followed the doctor's advice the previous day. The child succumbed to illness 24 hours later.

Post-death counseling in these situations can often be tricky. Parents willingly didn't want to harm their child but their actions (refusing admission 24 hours earlier) may have worsened their child prognosis. However, being entirely truthful in these circumstances is seldom beneficial. The caregiver can be guarded in answering parents' questions that would the child have recovered had they admitted the child on their first visit to ER by saying that he could have done better but no one could know that for sure. On the other hand, he did show some improvement after the antipyretics at that time, so he can understand why they decided of taking him home. Moreover, when the danger signs (seizure) appeared they immediately sought medical help. Speaking candidly in such circumstances may lead to guilt, self-blame, and regret in parents. This can lead to family conflict, depression and even separation among parents. The loss of a child is already a heartbreaking event for the family members, so it is inadvisable to further saddle the family members with unnecessary guilt.

Parents/family members in such cases should be provided with professional emotional and psychological supportfor several days/weeks to help them get over the loss of their child.

Points to Remember

- ***In this era, ordering right tests and prescribing right medications alone is not sufficient. counselling about disease condition is just as important.***
- ***Patient counselling is not like one-size-fits-all, every individual has a different way of reacting to unsettling news. Thus, a physician should evolve his counselling skills and use them according to the needs of his patient's family members.***
- ***Good communication improves a parent's adjustment to illness, lessens anxiety and fear, increases adherence to treatment, and results in higher rate of satisfaction. Poor communication skills are associated with increased use of ineffectual treatments by the parents, higher rates of conflict between parents and doctor and less adherence to doctors' advice.***
- ***A variety of communication tools and road maps can help clinicians find their way through difficult conversations.***
- ***Ultimately honesty is the best policy.***

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GENETIC TESTING IN CLINICAL PRACTICE - DIAGNOSTIC STEWARDSHIP

***Sankar VH**

Abstract: *Advances in the field of molecular medicine and genetic engineering have found applications in clinical practice in the form of diagnosis, treatment and prevention of genetic disorders. Cytogenetics refers to the description of chromosome structure and the identification of genomic aberrations that cause diseases. 'Fluorescence in situ hybridization' is a process whereby chromosomes or portions of chromosomes are vividly painted with fluorescent molecules that anneal to specific regions. Detecting the changes in DNA (mutation) responsible for the genetic disease is the diagnostic test for single gene disorders. 'Chromosomal microarray' is a high resolution, whole-genome screening technique that can identify most of the chromosomal imbalances detected by conventional cytogenetic analysis, as well as smaller sub-microscopic deletions and duplications that are referred to as copy-number variants that may be missed in the conventional karyotyping. 'Next generation sequencing' is a powerful platform that has enabled the sequencing of thousands to millions of DNA molecules simultaneously. This article review the rational use of various investigations used for the diagnosis of genetic disorders in clinical practice.*

Keywords: *Cytogenetics, Chromosomal microarray analysis, Next generation sequencing.*

The last decade has brought about a huge change in the outlook about molecular medicine and genetic engineering in their application for diagnosing, treating and preventing genetic disorders. Genetic disorders are traditionally categorized into three main groups: single-gene disorders, chromosomal disorders and multifactorial disorders. Single gene disorders are due to mutations in a single gene causing qualitative or quantitative defects in the protein. Chromosomal disorders are due to chromosomal aberrations including numerical and structural abnormalities. In multifactorial diseases, multiple genes are involved along with environmental factors that contribute to the onset of the disease. During evaluation of a suspected genetic disorder, apart from hematological, biochemical and radiological investigations,one has to use some specialized genetic investigations to arrive at a diagnosis.

Box 1. Indications for genetic testing

1. For accurate diagnosis in a child with genetic disorder to help in proper prognostication of the condition.
2. Prenatal diagnosis in the affected fetus.
3. Pre symptomatic genetic testing of high risk individuals likely to develop disorders e.g., Huntington's chorea, hereditary cancers harbouring TP53 mutations.
4. Carrier screening of the couple or an individual with family history of genetic disorder.

Genetic testing is used in various situations in clinical practice (Box 1). The most common and important indication for genetic testing is for the diagnosis of genetic disorder. An accurate diagnosis of the condition will help in the proper prognostication of the patient and will help in the prenatal diagnosis of other family members. Prenatal diagnosis testing in the fetal sample by chorionic villus sampling(CVS)/amniocentesis is the other indication of genetic testing where prior confirmation of genetic diagnosis in the affected child (proband) is mandatory. Carrier screening of the couple or an individual is another indication for genetic testing (e.g. carrier screening in an adult female with family history of Duchenne muscular dystrophy). Genetic testing is also useful in situations where the identification of high risk individuals to develop a disorder can be tested by pre symptomatic genetic testing (e.g. adult onset neurological disorders like Huntingtons disease and screening for TP53 mutation in a family with multiple members with hereditary cancers harbouring TP53 mutation). In all situations where genetic testing is done it should be accompanied by pre-test and post-test genetic counseling.

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Box 2. Indications for Karyotyping

1. Congenital malformation
2. Developmental disorders
3. Intellectual disability
4. Primary or secondary amenorrhea
5. Infertility
6. Recurrent spontaneous abortions
7. Previous child with a chromosomal abnormality

Cytogenetics methods

Cytogenetics refers to the description of chromosome structure and the identification of genomic aberrations that cause diseases. Numerical aberrations and structural anomalies can be detected by cytogenetic analysis. Karyotype refers to the ordered display of chromosomes starting from the largest chromosome to the smallest followed by the sex chromosomes based on the size, shape, centromere position and banding pattern Fig.1.(A) and Fig.1.(B).The indications for doing karyotyping are shown in Box.2.[1]

Structural chromosomal anomaly can be identified by band pattern in the chromosomes. In children with multiple malformations where a structural abnormality is identified, parental karyotype should be done to look for balanced chromosomal rearrangements. In balanced chromosomal rearrangement (translocation) there is no loss or gain of chromosome material, whereas in case of unbalanced translocation the exchange of chromosome material is unequal resulting in extra or missing genes. Balanced translocations are usually harmless but the carriers of balanced reciprocal translocations have increased risks of creating gametes with unbalanced chromosome translocations, leading to infertility, miscarriages or children with abnormalities. Fig.2.(A) and Fig.2.(B) shows a child with multiple malformations having

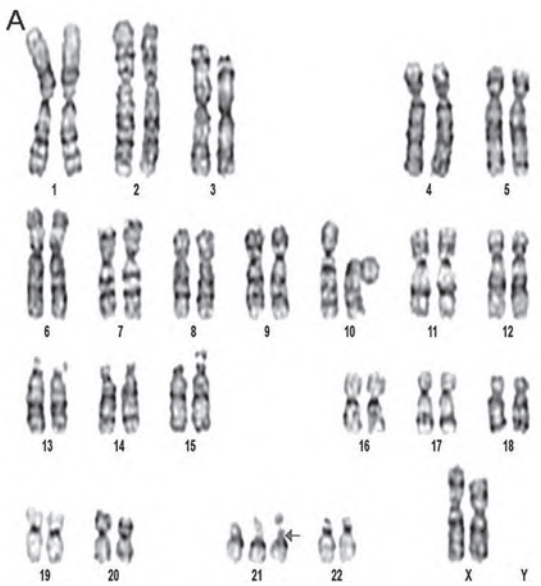

Fig.1.(A) Conventional karyotyping Down syndrome showing trisomy 21 (ISCN:47,XX+21)

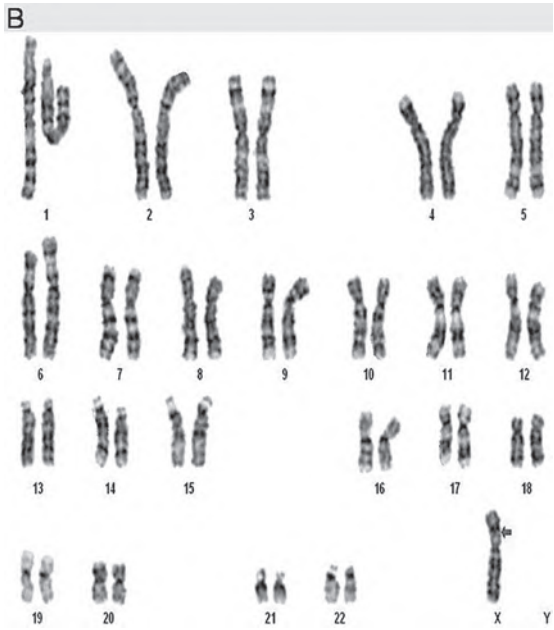

Fig.1.(B) Girl with short stature showing monosmy X confirming Turner syndrome (ISCN:45X) (ISCN International system for cytogenetic nomenclature)

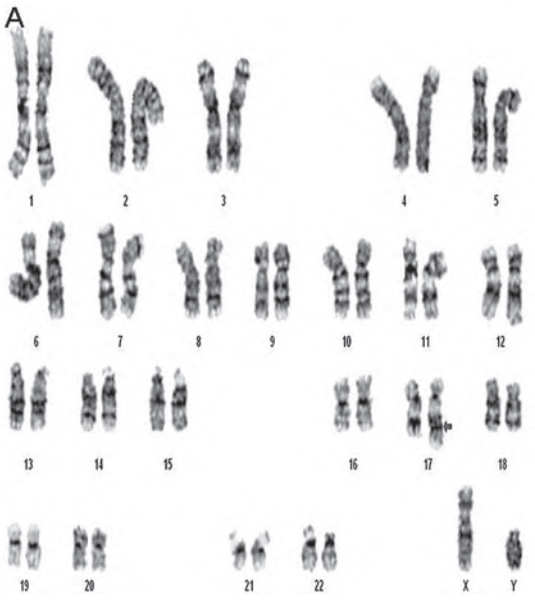

Fig.2.(A) Conventional karyotyping of child with multiple malformations (A) structural abnormality involving chromosome 17

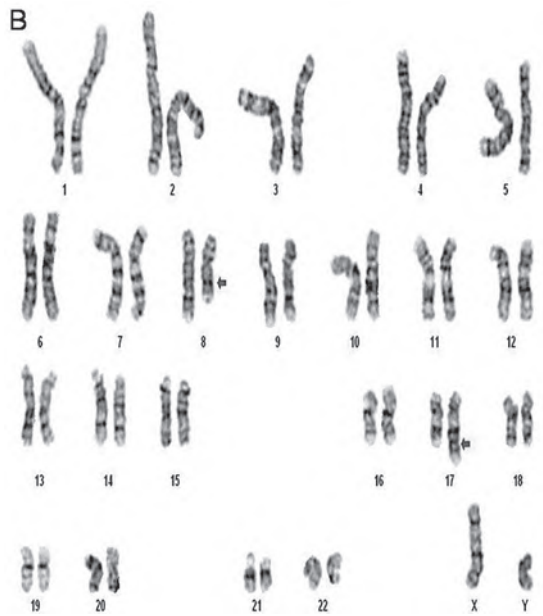

Fig.2.(B) father having a balanced translocation involving chromosome 17 and chromosome 8.

an unbalanced translocation and his father harbours a balanced translocation.

The major limitation of conventional cytogenetic method is that the chromosomal aberration should be large enough, at least 5-10Mb size to be detected microscopically.[1] Small sub-microscopic alterations below 5Mb cannot be picked up by this method. Moreover, banding analysis is considered to be time consuming and labour-intensive. Limited chromosome-specific banding resolution makes the characterization and correct interpretation of complex and cryptic chromosome alterations difficult to ascertain. Many of the genetic disorders have mutations involving only one or very few nucleotides which are not analysable by karyotyping but special cytogenetic tests can overcome this limitations.

In order to overcome the limitations of conventional cytogenetic analysis, various molecular cytogenetic techniques such as fluorescent in situ hybridization (FISH), spectral karyotyping (SKY), M-Fish and comparative genomic hybridization (CGH)/ Microarray have emerged as successful diagnostic tools and are widely used as accompaniment to classical cytogenetics for identifying chromosomal aberrations.[2] Fluorescent in situ hybridization (FISH) is a process whereby chromosomes or portions of chromosomes are vividly painted with fluorescent molecules that anneal to specific regions and has many uses (Box 3).[3]

Box 3. Uses of FISH

1. Aneuploidy screening in prenatal specimens
2. Evaluation of gene rearrangements in hematological malignancies
3. Microdeletion syndromes
4. Rearrangements of subtelomeric regions
5. To identify genes with increased copy number

When compared to cytogenetics which require banded and well spread metaphases for analysis, FISH can be

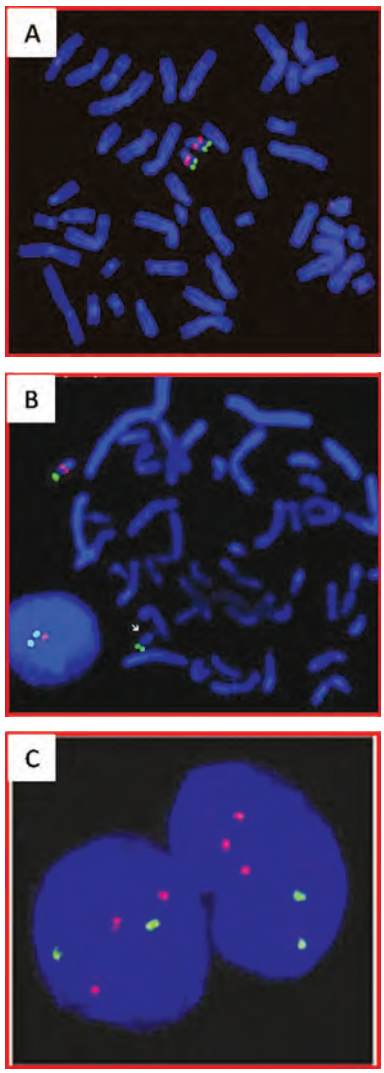

Fig.3. Metaphase FISH: Locus specific probe (red) for 22q11 deletion and control probes (green) showing in (A) Normal individual (B) in a child with 22q11 deletion syndrome (C) Interphase FISH showing Trisomy 21(red) and control probe (Green) during rapid aneuploidy testing.

performed in both metaphase and interphase cells (Fig.3). FISH is highly sensitive and specific and can be performed rapidly. At the same time the disadvantage is that only one or a few abnormalities can be assessed simultaneously based on the number of FISH probes used for the detection. Moreover, it is possible to detect only the known aberrations e.g. microdeletion of a particular gene (specific probe for 22q11 deletion syndrome), translocation, sub-telomeric deletion, detection of aneuploidy, etc. involved with specific disease condition depending on the probes designed.

Chromosomal microarray analysis (CMA) is a high resolution, whole-genome screening technique that can identify most of the chromosomal imbalances detected by conventional cytogenetic analysis, as well as smaller sub-microscopic deletions and duplications that are referred to as copy-number variants (CNVs). CMA is recommended as the first-tier test in the postnatal evaluation of congenital abnormalities and neurodevelopmental disorders.[4,5]

The main advantage of this technique is that it can identify cryptic imbalance at the break points which otherwise appears as an apparently balanced translocation by classical cytogenetics. The extra or additional regions attached to the chromosomes can be easily delineated through this method. Likewise an extra chromosome of unknown origin (a marker chromosome) can be clearly identified. The resolution of this method is 1-5 Mb, but can be increased up to approximately 50-100Kb level. Another advantage of CMA is that this technique does not require dividing cells, in contrast to conventional karyotyping, which requires cell culture.Limitations of this technique includes the difficulty in detecting balanced translocation, inversions, low level mosaicism and whole genome ploidy.[2]

Molecular genetics methods

Human genome contains 3,000,000 base pairs and large number of variants were identified which may be normal polymorphic variants or disease causing variants (mutations).[6] When the variants are associated with a genetic disorder, they are referred as pathogenic variants. The aim of molecular genetic testing is to detect small variants, such as: single base pair changes, small insertions/ deletions, large intragenic rearrangements or change in the copy number of triplet repeats. There are different

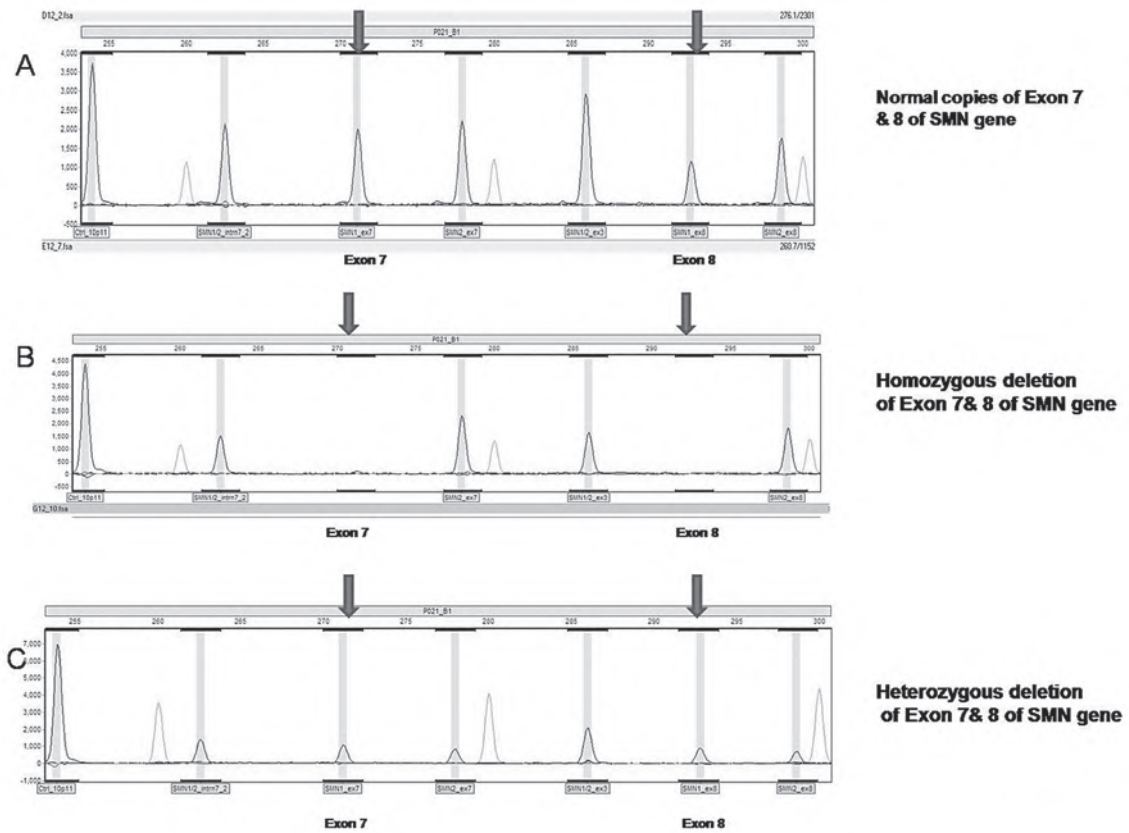

Fig.4. MLPA for spinal muscular atrophy showing (A) Normal individual (B) person with spinal muscular atrophy showing homozygous deletion of exon 7 and exon 8 of the SMN gene and (C) person with carrier status showing heterozygous deletion of exon 7 and exon 8 in SMN gene.

molecular techniques to identify the pathogenic variants and their rational use in the appropriate clinical situation is important.

Polymerase chain reaction (PCR): PCR is the basic step for many molecular methods, which is a technique used to amplify DNA fragment of interest to millions of copies [amplicon] in a few hours from an initially small sample, sometimes even from a single copy. PCR fragments can be visualized by performing gel electrophoresis. The simplest clinical application of PCR is Y chromosome deletion studies, which will detect the deletions in the long arm of the Y chromosome known to be associated with male infertility.[7] The limitation of polymerase chain reaction is that, a prior information about the target sequence is necessary in order to generate the primers that will allow its selective amplification. Most PCR methods amplify DNA fragments of between 0.1 and 10 kilo base pairs (kbp) in length, So, if the gene is very large it is difficult to detect the mutation by conventional PCR.

Restriction fragment length polymorphism (RFLP): This method is based on using restriction enzymes with ability to cut DNA at short, specific sequences called restriction sites. Point mutations (mutation that only affects a single nucleotide) in this region can change restriction site in DNA causing alteration in cleavage by restriction enzyme which produce fragments with various sizes. RFLP method is used to detect the point mutation in sickle cell disease and achondroplasia.[8] One of the major disadvantage of this technique is that it can be done only to detect known point mutation and many samples cannot be analysed in a short time.

Multiplex ligation-dependent probe amplification (MLPA): MLPA is simpler, more sensitive and less time intensive when compared to other traditional techniques for the detection of deletions and duplications. This is a modification of multiplex polymerase chain reaction by which amplification of multiple targets are possible with only a single primer pair. MLPA has a variety of applications including detection of deletions/duplications, single nucleotide polymorphisms, analysis of DNA methylation, relative mRNA quantification, chromosomal characterisation of cell lines and tissue samples, detection of gene copy number and aneuploidy determination.[9] MLPA has potential application in prenatal diagnosis also. More than 300 probe set are commercially available targeting different genetic conditions like spinal muscular atrophy, Duchenne muscular dystrophy and microdeletion syndrome (Fig.4).

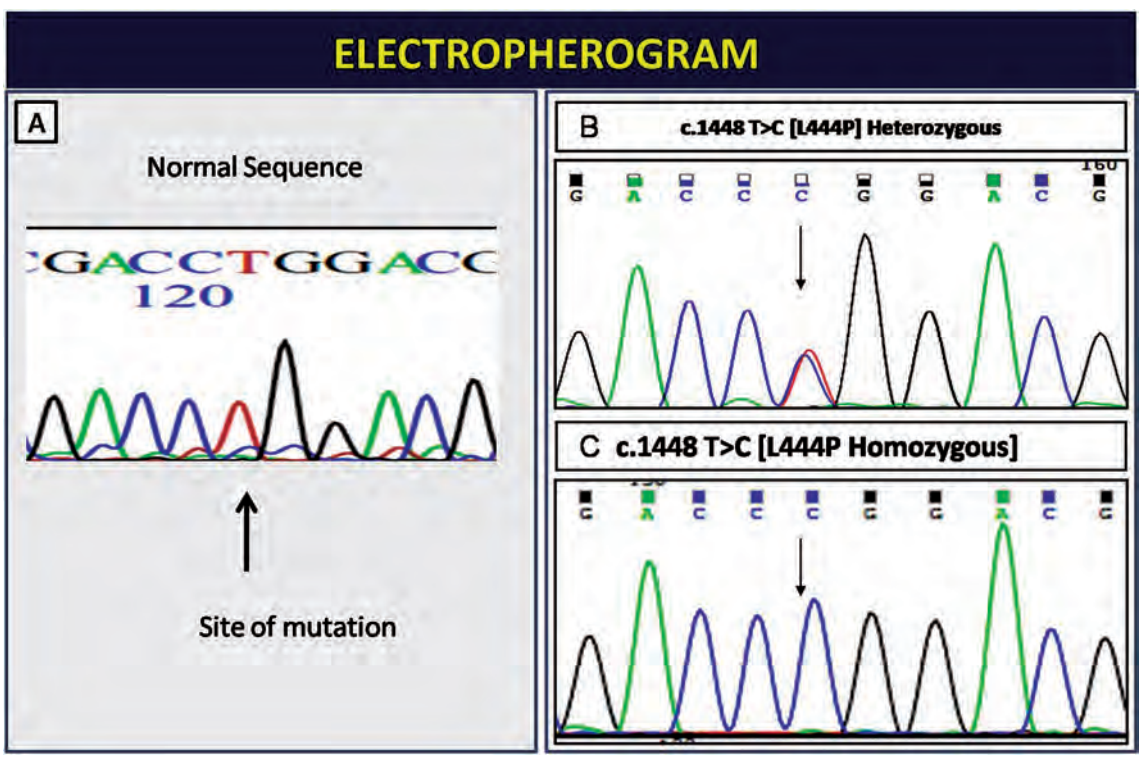

Fig.5. Electropherogram after Sanger sequencing for Gaucher disease showing (A) sequence in a normal individual (B) common mutation c.1448C>T in heterozygous individual showing two peaks and (C) change in the nucleotide T (red) to C (Blue) in the particular position in affected child with Gaucher disease.

An electropherogram is a chart produced when electrophoresis is used in an analytical technique. In genetics, it is used for genotyping such as DNA sequencing, based on the length of specific DNA fragments.

Single gene sequencing by Sanger sequencing: Once the gene of interest is amplified by any of the PCR methods, the final confirmation regarding the nucleotide variation is done by automated Sanger sequencing, which is the most widely used technique for sequencing DNA that allows the detection of nucleotide sequence [A,T,G,C] in a short fragment of DNA [(~1 kilo base)] using PCR product as a template. Automated DNA sequencers generate a four-color chromatogram (each colour corresponds to each nucleotide) showing the results of the sequencing (Fig.5). Sanger sequencing can detect most common mutations that affect coding sequences (e.g. missense and nonsense point mutations, small insertions/deletions and mutations involving the splice site junctions i.e. intron-exon boundary). It is considered as the gold standard for detecting these small sequence changes in a gene. This method can be applied to detect variants in all the 3 exons of the HBG gene associated with beta thalassemia. This method would not detect large insertions/deletions, copy number variations, or nucleotide repeat expansions. Other major limitations include low throughput, high cost, very laborious and expensive especially when large genes are to be tested with heterogeneous mutations (Marfan syndrome, neurofibromatosis) or when more than one gene for the same phenotype (muscular dystrophy) has to be tested.

Real time PCR or quantitative PCR (qPCR): Real-time PCR has become one of the most widely used methods of gene quantification. Real-time PCR make use of fluorescent probes or dyes which emit fluorescence when there is amplification of the template. It monitors the amplification of a targeted DNA molecule during the PCR (i.e., in real time), not at its end, as in conventional PCR. Nucleotide sequence changes (point mutations) and gene dosage/copy number variations (deletions or insertions/duplications) that causes human monogenic diseases can be detected by this method. This technique is widely used for gene expression studies especially to detect the viral load in hepatitis B and HIV. Real time RT-PCR is one of the most widely used laboratory method for detecting the COVID-19 virus.[10] Here, the real time PCR is combined with reverse transcription - polymerase chain reaction [RT-PCR] since corona virus is a RNA virus. The real time RT-PCR technique is highly sensitive, specific and significantly faster and has a lower potential for contamination or errors as the entire process can be carried out within a closed tube within three hours.

Methylation PCR: DNA methylation pattern in CpG islands is an essential mechanism by which the cell regulates gene expression of imprinted genes. Prader Willi syndrome (PWS) and Angelmann syndrome (AS) are two distinct neurodevelopmental disorders due to the loss of expression of imprinted genes. Methylation specific PCR at the Small nuclear ribonucleoprotein-associated protein N (SNRPN) locus is the first diagnostic test to be performed in these conditions. This will detect 99% of individuals with PWS and 80% individuals with AS.[11] Normal controls will have both bands amplified while PWS-affected patients will have only a maternal band and AS-affected patients will have a paternal band.

Triplet primed repeat PCR (TP-PCR): Trinucleotide repeat disorders are a set of genetic disorders caused by trinucleotide repeat expansion in certain genes that exceed the normal, stable threshold of a gene. In general, an increasing number of repeats results in more severe phenotypes and the number of repeats increase (expand) as the disease gene is inherited. This is widely used for the detection of Friedreich's Ataxia (FRDA), myotonic dystrophy type 1 (DM1), spinocerebellar ataxia (SCA), fragile X syndrome (FRAXA) etc.[12] TP-PCR is robust, reliable and inexpensive and can be used to screen large series of patients, although it cannot give a precise evaluation of the size of the expanded allele. This test may be of practical value in prenatal diagnosis also.

Quantitative fluorescence-polymerase chain reaction (QF-PCR): QF-PCR is a quantitative and faster technique than the traditional karyotype method for the detection of aneuploidy. QF-PCR is highly applicable in the field of prenatal diagnosis for the rapid diagnosis of chromosomal aneuploidy which accounts for approximately 53% of all chromosome abnormalities and is the most frequent genetic disorder observed in live births and miscarriages, with trisomy being the most prevalent. The obvious candidates in whom these new technologies can be applied are the high risk patients (those with fetal malformations/soft markers or advanced maternal age).

Next generation sequencing (NGS): Next generation sequencing (NGS) also known as high-throughput sequencing is a powerful platform that has enabled the sequencing of multiple genes by massive parallel sequencing.[13] Currently three main levels of analysis can be performed by NGS: disease targeted gene panels, whole exome sequencing (WES) and whole genome sequencing (WGS). The raw data out of the NGS platform should undergo a very complex bioinformatics analysis collectively called as "pipeline" and variant interpretations.[14] Disease targeted gene panels investigate

Table I. Common clinical scenario in clinical practice and rational genetic tests in the situation

Clinical scenario	Rational genetic tests
Characteristic chromosomal abnormalities like Down syndrome, Turner syndrome, Klinefelter syndrome, etc	Conventional karyotype
Parents of a child with chromosomal abnormalities, couple with the recurrent pregnancy loss, infertility	Conventional karyotype
Microdeletion syndrome (Di George syndrome, William syndrome), Rapid aneuploidy testing in prenatal sample	Fluorescent in situ hybridization (FISH)
Multiple malformation, intellectual disability, autism spectrum disorders	Microarray
Single gene disorders with specific point mutation like sickle cell disease, achondroplasia	Restriction fragment length polymorphism (RFLP) based PCR technique for specific mutation
Single gene disorders with deletion/duplication of exons like spinal muscular atrophy and Duchenne muscular dystrophy	Multiplex ligation dependent probe amplification (MLPA)
Single gene disorders with different type of mutation in a single gene like Thalassemia and cystic fibrosis	Sanger sequencing of the entire gene
Single gene disorder due to trinucleotide repeat mutations like Huntington's chorea and fragile X syndrome	Triplet prime PCR (TP-PCR)
Hemophilia A to detect inversion mutation	Inverse PCR
Viral infection like COVID-19 and hepatitis B	RT-PCR (for RNA virus) and Real time PCR for viral load determination
Rapid prenatal diagnosis for aneuploidy detection	Quantitative florescent PCR (QF-PCR)
Single gene disorders with different mutations in different patients (private mutation) like neurofibromatosis, same phenotype with mutation in a multiple genes like deafness and muscular dystrophy	Next generation sequencing (NGS) based panel testing with multiple gens or clinical exome sequencing
Specific phenotype probable genetic disorder not fitting into known genetic disorder and other common genetic testing does not shown any abnormality	Whole exome sequencing (WES) and whole genome sequencing (WGS)

a number of different genes associated with a particular phenotype. Focused panels contain a select set of genes or gene regions that have known or suspected associations with the disease or phenotype under study.

Clinical exome sequencing (CES) is a new state-of-the-art molecular diagnostic genetic test which detect disease-causing genetic mutations within any gene identified as a cause for genetic disease [OMIM listed genes] in the human genome more rapidly and efficiently and is therefore becoming widely used in clinical practice.

Whole genome sequencing (WGS) attempts to cover both coding and noncoding regions, however determination of pathogenicity of the variants detected may be very challenging and is recommended only in research studies. About 85% of disease-causing mutations in Mendelian disorders are located in coding regions. The coding sequences [exons] accounts for 1% (30Mb) of the whole genome. In whole exome sequencing (WES) more than 95% of the exons [coding sequences] are covered. Sequencing of the complete coding regions (exome), could potentially uncover the mutations causing rare, mostly monogenic, genetic disorders as well as predisposing variants in common diseases and cancer. WES will identify the diseases causing variants in approximately 25% of the previously undiagnosed cases. Even though NGS is the

most advanced technique, it is still not an all comprehensive approach and significant limitations exist.

Summary

The genetic testing in any given clinical situation is to be considered in the light of three factors: Analytical validity, clinical validity and clinical utility. Analytical validity is the test accuracy in which, whether the specific test correctly detect the pathogenic variation (mutation) associated with this genetic disorder can be found. Clinical validity refers to the degree to which the test correctly predicts presence or absence of the disease. Clinical utility refers to the degree to which the specific genetic test helps the clinician in clinical decision making and management. Common clinical scenario with specific genetic testing is summarised in Table I. Every clinician should practice "Diagnostic stewardship" in the selection of these expensive genetic testing and pre-test counselling should be an integral part of genetic testing.[15]

Points to Remember

- ***The indications of genetic testing include diagnosis of genetic disorders, prenatal diagnosis, carrier testing and pre symptomatic diagnosis.***
- ***Genetic testing in clinical situation should be accompanied by pre-test and post-test genetic counselling.***
- ***Cytogenetic methods include conventional cytogenetics, FISH and microarray which can detect chromosomal aberrations and copy number variants.***
- ***Rational selection of molecular methods depends on the type of mutation to be tested in the specific genetic disorder.***
- ***Always consider the three principles – analytical validity, clinical validity and clinical utility when considering a specific genetic test in a given clinical scenario.***

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LIMPING CHILD

***Sankar R**

Abstract: *Painful or painless limp or gait disturbances are one of the most common problems encountered in general pediatric practice. The cause for this condition can be benign to life threatening. Thorough history taking with examination along with appropriate investigations help pediatricians to manage children with limp. This article aims to help practicing paediatricians differentiate various causes and approach to investigation and care of the same.*

Keywords: *Limp, Osteomyelitis, Septic arthritis, SCFE.*

Limp is an abnormal gait which can be caused by pain, muscle weakness or joint and bone deformities of lower extremities. It may be due to simple self-limiting conditions like muscle sprain to serious life threating conditions like malignancies. Prompt diagnosis and management is necessary to avoid long term morbidity and mortality.

Incidence of limping in children is unknown. Fischer et al in their study reported majority of cases were related to trauma, an acute atraumatic limp is reported to be at a rate of 1.8 per 1,000 children below 14 years, with male to female ratio of 1.7:1 and a median age of 4.4 years. Limp was mainly right sided (54%) and 80 percent of the children reported pain at the time of presentation. Less than 50% of children had preceding illness. Transient synovitis was the most common diagnosis.[1]

Examination of the child should start with detailed history from parents, focusing on the presence of pain, history of trauma, or any associated constitutional symptoms.[2]

Pain

Limp can present as painful or painless limp. Painless limp does not require urgent evaluation, whereas painful limp should be treated as an emergency. Pain associated with limp may usually be due to injury or infection. Pain that is constant, localizing and reproducible usually represents a fracture, osteomyelitis, or septic arthritis. Children may also have referred pain to the knee from disorders of the hip such as Perthes' disease or slipped capital femoral epiphysis (SCFE). Back pain or thigh pain may indicate lumbar spine disorders. Children complaining of pain only at night may be due to osteoid osteoma.

Duration

Duration of the limp can help to differentiate between acute versus chronic conditions. Typically, acute onset of limp is due to trauma or an infection, whereas insidious onset of symptoms may be more indicative of Perthes' disease, SCFE, or a rheumatologic aetiology.

Age

Age of the child at the time of presentation helps to narrow the diagnosis (Table I). Developmental dysplasia of hip (DDH) is commonly seen up to age of 3 years whereas Perthes disease, JIA and leukaemia should be considered among children between 4 and 10 years. Joint sprains, overuse syndromes, SCFE and tumours should be considered in the adolescent age group.

Systemic illness

Presence of fever, loss of weight and appetite and night pain suggests the possibility of infection, inflammation, or malignancy rheumatologic and oncologic conditions such as Juvenile inflammatory arthritis (JIA) and leukemia, are less commonly associated with fever but should be considered in the differential diagnosis in the presence of systemic symptoms such as loss of weight and appetite, bone pain or fatigue.

Physical examination

A thorough physical examination with the child completely undressed should be performed on all children presenting with a limp. The gait of the patient should be assessed while walking bare feet. Look for erythema, swelling, or signs of trauma such as abrasions or lacerations. The feet, legs, hips and back should be palpated to elicit tenderness. or masses.

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Table I. Common causes of limping in various age groups

All ages		
• Trauma (fracture, hemarthrosis, soft tissue) • Infection (septic arthritis, osteomyelitis, discitis) • Secondary to various viral illnesses • Tumour • Sickle cell disease • Serum sickness		
Toddler (1-3 years)	**Child (4-10 years)**	**Adolescent (11-16 years)**
• Transient synovitis • Toddler‘s fracture • Developmental dysplasia of hip • Neuromuscular disease • Hemophilia	• Transient synovitis • Juvenile arthritis • Perthes disease • Rheumatic fever • Haemophilia	• Slipped upper femoral epiphysis • Overuse syndromes • Osteochondritis dissecans

Examination of the back for curvature and point tenderness along with sacroiliac joints are also an important aspect of the physical examination. A complete neurologic examination assessing for tone, reflexes, presence of clonus or loss of sensation should be done to rule out central or peripheral nervous system disorders. Passive and active range of motion of joints should be assessed and compared to the opposite side. Specific clinical tests may have to be performed to confirm or rule out specific cause for a limp.

For the Trendelenburg test, the child stands on the affected leg and the observer looks for the drop of the pelvis toward the unaffected side. A positive test indicates disorders of the hip such as DDH, LCP disease or SCFE. In the Galeazzi sign test, the child lies in the supine position with both hips and knees flexed. The practitioner observes heights of the knees and if one side is lower than the other, the test is positive, revealing a limb-length discrepancy with the lower side shorter than the other.

The Flexion, abduction and external rotation test is performed by having the child lay supine while the examiner flexes, abducts and externally rotates the hip joint. If this results in hip pain or limitation of flexion, it implies a disorder of the sacroiliac joint.

Investigations

The differential diagnosis considered in a child will help to decide the laboratory tests to be performed. When an infectious or inflammatory cause for the limp is suspected on clinical evaluation, laboratory tests to be considered include a complete blood count (CBC), blood culture and acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

A clinical guideline developed by Kocher et al., proposed that a history of fever, non-weight-bearing on the affected side, ESR >40 mm/hr, and serum white blood cell count of >12,000 cells/mm^3 is indicative of septic arthritis as opposed to transient synovitis. They found that if only 1 of the 4 was present, the predicted probability for septic arthritis was about 3%, but it increased to 99% when all four criteria were present.

Radiography and ultrasonogram (US) of the hip are the commonly used imaging modalities to evaluate a child with limp.[3] X-ray of the hip is particularly useful in the diagnosis of DDH, Perthes' disease and SCFE, whereas US of the hip is useful when septic arthritis is suspected.

Initial X-ray may be normal in children with stress fractures, toddler's fracture, osteomyelitis or septic arthritis. Ultrasonogram is highly sensitive for detecting effusion in the hip joint, but it cannot differentiate between transient synovitis and septic arthritis.

Magnetic resonance imaging (MRI) has been used with high frequency to evaluate children with suspected acute or chronic osteomyelitis. MRI is also very useful in diagnosing discitis. A computed tomography (CT) scan is helpful in diagnosing chronic osteomyelitis as it clearly demonstrates cortical destruction as compared with MRI. CT scan also is useful in diagnosing benign and malignant bone lesions.

Transient synovitis hip

One of the most common cause of limp in children between 3 and 8 years. Child presents with acute onset of hip pain with limited range of movements. There may be

history of recent viral illness. Even though it may look like septic arthritis, child will not have fever or systemic illness. WBC and CRP will be normal and symptoms settle with rest and analgesia.

Septic arthritis

Children with infection in any joint requires urgent surgical treatment because of the potential for significant joint destruction. Child will have acute onset of pain with limp. They will have fever, chill and malaise. Movement of the affected joint will be very painful. WBC and CRP will be raised.

Osteomyelitis

In toddlers and children, osteomyelitis presents with localised swelling, pain and pseudo paralysis with fever. Any children presenting with bone pain with fever is treated as osteomyelitis until proven otherwise. Once confirmed with blood reports, to start intravenous antibiotics. If it doesn't settle within 36 hours, it needs surgical management.

Juvenile idiopathic arthritis

Pauciarticular JA is most common. Child will present with painless effusion. Child will have mild limp with decreased range of movement.

Developmental dysplasia of hip

It causes painless limp in children, affected leg will be short compare to other leg. If bilateral, child walks with waddling gait. In neonatal period, diagnosis is made with clinical examination followed by ultrasound hip examination. If diagnosed early, it can be treated with Pavlik harness. Late diagnosis will result in open reduction.

Perthes' disease

Avascular necrosis of femoral head leads to pain and limp. It occurs between 2-10 years, more common in boys, 10-15% children will have bilateral involvement. X-ray and MRI will help to diagnose and stage the disease. Most cases settle with rest.

Slipped capital femoral epiphysis

Most common disorder in adolescents. Children with endocrinopathy are more prone to slip. More common in boys than girls. 25% of children will have bilateral involvement. They will present with limp, pain and difficulty in weight bearing. Urgent surgical intervention is required to prevent disability at a later stage.

Points to Remember

- ***Causes of limp varies with age.***
- ***Fever with painful limp needs urgent evaluation.***
- ***Adolescent with acute onset of limp needs investigation to rule out slipped capital femoral epiphysis.***

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CLIPPINGS

Pediatric headbox as aerosol and droplet barrier

High-flow nasal oxygen (HFNO) is frequently used in hospitals, producing droplets and aerosols that could transmit SARS-CoV-2. To determine if a headbox could reduce droplet and aerosol transmission from patients requiring HFNO. Methods -The size and dispersion of propylene glycol(model for patient-derived infectious particles) was measured using a spectrometer and an infant mannequin receiving 10–50 L/min of HFNO using (1) no headbox, (2)open headbox, (3) headbox-blanket or (4) headbox with a high-efficiency particulate (HEP) filter covering the neck opening. Results All headbox set-ups reduced the dispersal of droplets and aerosols compared with no headbox. The headbox-blanket system increased aerosol dispersal compared with the open headbox. The fraction of aerosols retained in the headbox for HFNO of 10 and 50 L/min was, respectively, as follows: (1) open headbox: 82.4% and 42.2%; (2) headbox-blanket: 56.8% and 39.5%; (3) headbox-HEP filter: 99.9% and 99.9%. Conclusion A HEP-filter modified headbox may serve as an effective droplet and aerosol barrier adjunct for the protection of staff caring for children receiving HFNO.

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DEVELOPMENTAL ASSESSMENT OF A 10 MONTHS OLD INFANT

Somasundaram A

Abstract: *Development of a child is assessed in office practice by simple observation. The way a child plays, learns, speaks, acts and moves offers important clues about the child's development. Developmental milestones are the skills acquired by a growing child at appropriate ages. Even a normal child without any risk factors, who is expected to follow a normal path, should undergo periodic developmental screening. In the absence of established risk factors or parental or provider concerns, a general developmental screen is recommended at 9-18 and 30-month visits. A ten-month old will usually enjoy his new found freedom through an exploration drive and hand-eye coordination which will help him to grasp the objects quickly. The child displays social abilities and emotional temperament and also understands the importance of the social gesture of waving bye-bye. It can imitate basic actions and also displays separation anxiety.*

Keywords: *Developmental assessment, Milestones, Pincer grasp, Object permanence.*

"I regard developmental assessment as an essential part of everyday practice with a minimum of equipment in an ordinary mixed clinic and not in a special room, at a special time, or with special complicated equipment. Everyone dealing with children needs this knowledge"
-Dr Ronald S Illingworth

Every age specific milestone has got a range during which the normal children acquire that milestone. It is necessary to make sure that the baby can see and hear before we proceed with the developmental screening/assessment. The ideal environment for developmental milestone check is given in Fig.1.

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Corrected gestational age

In preterm babies, always check developmental milestones for the corrected gestational age till 2 years of life.

CGA[Corrected gestational age] = CA [Chronological age] - No of weeks/months born premature

Importance of 10th month - a turning point in child development

At 10 months, many babies make progress on new developmental milestones such as standing, stacking items, and feeding themselves.

1. Many issues involving motor skills development can be reliably identified.
2. Early communication skills may be emerging-evidence suggests symptoms of autism, such as lack of eye contact, orienting to name being called, or pointing, may be recognizable at 10th month of life.
3. Social and nonverbal communication, including vocalizations and gestures, are important aspects of emerging communication that can be assessed at 10 months.
4. The child starts exploring and has better coordination in its activities.

Domains of development

Typical development is often considered in five broad areas although clearly they overlap to an extent.

- Gross motor.
- Fine motor and vision.
- Hearing and speech.
- Social development.
- Cognitive development.

The child is assessed in each domain and the most important developmental milestones at 10 months are summarised in Table I.

Pincer grasp

Children learn to use the index finger as a separate "pointer finger" and to use the index and thumb together

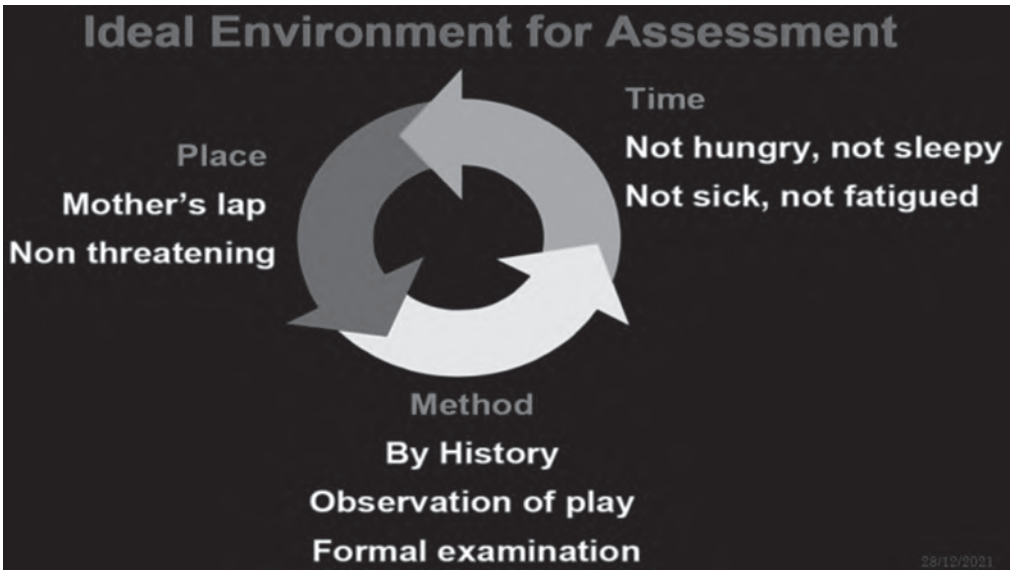

Fig.1. Ideal environment for assessment

Table I. Most important milestones at 10 months

Domain	Activities
Gross motor	• can pull self to sitting position. • sits steadily with little risk of overbalancing. • can stand holding on to furniture and collapses with a bump.
Fine motor	• picks up things like raisin or puffed rice between thumb and index finger [pincer grasp] • moves things smoothly from one hand to another • bangs 2 cubes
Language and communication	• understands "no" • makes bisyllables like"mama" "dada" and "baba" • uses fingers to point at things
Social and emotional	• copies sounds and gestures of others [imitation] • waves bye-bye. • plays pat-a-cake • afraid of strangers
Cognitive	• looks for things which are hidden [object permanence] • watches the path of something as it falls

in a "pincer grasp". Opposition of the thumb sets the stage for the sophisticated use of the hand characteristic of humans. The pincer grasp is used naturally only with visual coordination. The development of grasp is depicted in Fig.2. The child can easily transfer objects from one hand to another (Fig.3).

Imitation of gestures and sounds

The 10th month old can mimic and repeat the actions of others (Fig.4).

Object permanence

Object permanence is the concept that things remain, or continue to exist, even though the child cannot see them. The first signs of object permanence appear at two to three months of age when a child will briefly glance after an object that is removed from sight. The child then learns to search for a partially hidden object and by the age of 10 months will search for an object that is being completely covered by a cloth. At this stage, although mother leaving the room might lead to crying, the baby will begin to realize

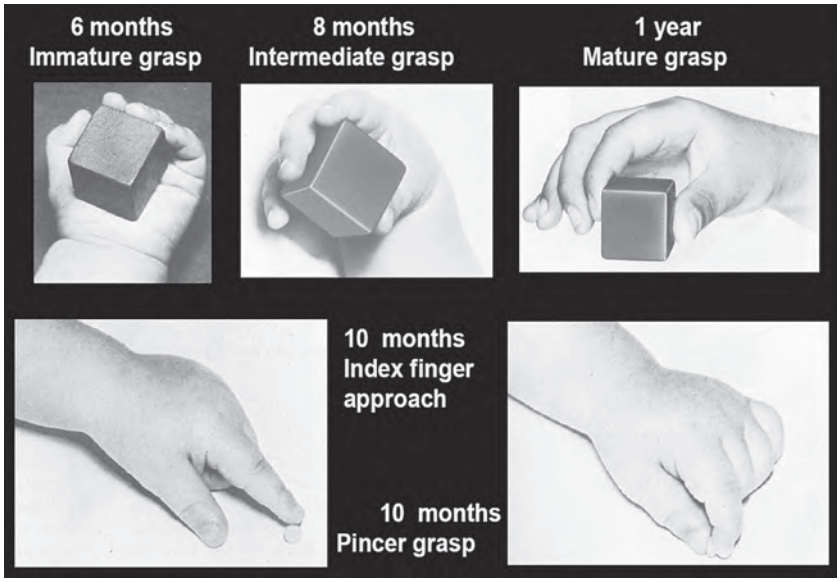

Fig.2. Pincer grasp

Fig.3. Moves things smoothly from one hand to another

Fig.4. imitates the gestures of others

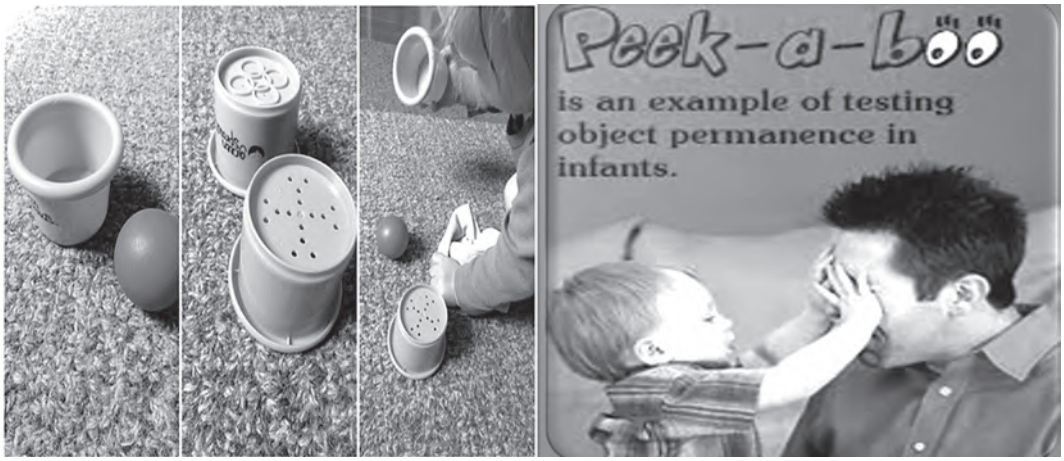

Fig.5a **Fig.5b** **Fig.5c** **Fig.5d**

Fig.5a. Cup and ball separately kept; Fig.5b. Ball covered by cup; Fig.5c. Baby removes the cup and identify the ball; Fig.5d. Peek-a-boo

that she is still around even when she is out of sight. Peak-a-boo is a game that helps to develop object permanence (Fig.5a to Fig.5d).

Testing for vision and hearing

Vision

Even though formal vision tests can't be done at 10 months, we can use certain activities which the child does at 10 months to check adequacy of vision.

Hand transfer, picking up objects between the thumb and index finger, stranger anxiety and taking finger foods to the mouth give a suggestion that vision is intact.

Hearing

All infants should be screened for their ability to hear, and a rough hearing test should be part of the routine examination. We can test for hearing by crumpling paper out of sight, on a level with the ear, about 18 inches away. Note particularly the rapidity of the response on each side. The disabled or deaf child is likely to be slow in responding.

In a 10-month-old, babbling and repeating the sounds "mama" "dada" and waving bye -bye on oral request gives a rough clue about adequate hearing. The child's obvious reaction to certain sounds or his understanding of familiar speech sounds in *tete-a-tete* conversation does not mean that the child could not have a hearing loss. When deafness is suspected, only a complete test is conclusive.

When to refer for early intervention?

- Doesn't bear weight on legs with support
- Doesn't sit with help
- Doesn't babble ("mama", "baba", "dada")
- Doesn't play any games involving back and forth play
- Doesn't respond to his own name
- Doesn't seem to recognize familiar people
- Doesn't look where you point
- Doesn't transfer toys from one hand to the other

Points to Remember

- ***Developmental problems are the "new morbidity in childhood".***
- ***Developmental screening should be part of a routine pediatric practice.***
- ***Attainment of mobility from 9 months onwards helps the child to explore***
- ***Object permanence, pincer grasp and vocalising bi syllables are the few milestones which develop at 10 months.***
- ***Early identification of red flags and timely referral helps in early intervention.***

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JUNCS

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Abstract: *Globally there is a rising trend in consumption of undesirable foods among children in the last few decades. There are multiple reasons for this, including changing demographic patterns, increasing urbanization, affordability and easy availability of these foods. The acronym "JUNCS" has been coined to include a variety of unhealthy foods. Considering the various ill effects, there is an urgent need to curb the consumption of "JUNCS", especially among children.*

Keywords: *JUNCS, Caffeinated drinks, Fruit drinks, Negative effects.*

Around the world, consumption of processed foods and other unhealthy foods has increased to dangerous proportions in the last few decades. This trend is observed in Indian children too. A food can be undesirable in many ways: (a) nutrient content (in terms of calories, saturated and trans fats, sugar, or salt) (b) quality (in terms of processing, packaging, preservation, preparation or storage), (c) having the potential to be consumed in large amounts because of its hyper palatability and (d) containing toxic substances. A recent survey from India has demonstrated that majority of our children are consuming one or other forms of such foods on a daily basis.[1] Childhood and adolescence are critical periods for physical, social and emotional development and it is highly desirable that healthy eating habits be established then.

Various terminologies exist that denote unhealthy foods like fast foods, junk foods, ultra processed foods, high fat, high salt/sugar (HFHSS) foods, etc. A national consultative group with various stakeholders in the private and public sectors was convened by the Nutrition Chapter of Indian Academy of Pediatrics (IAP). This group coined an acronym '**JUNCS'** to include a wide variety of unhealthy foods (Box 1).[2]

Box 1. JUNCS

J- Junk foods (foods high in fats, especially saturated and trans fats, sugars, salts and foods lacking in micronutrients/minerals).

U- Ultra processed foods (use many ingredients including food additives that improve palatability, processed raw materials and ingredients rarely used in home cooking like soy protein.

N- Nutritionally inappropriate foods (prepared in recycled oil, or contain high amount of sugar, fat or salt. Home-made foods with these characteristics can also be included in this group)

C- Caffeinated/colored/carbonated beverages.

Factors influencing increased intake of undesirable foods[3]

Various factors influence increased intake of JUNCS. Adolescents and young adults who form a sizeable proportion of the Indian population, are more inclined towards consuming fast-foods. Increasing urbanization leading to easy availability of fast foods and beverages through different apps and online platforms, increased affordability from more disposable incomes with expanding middle class and increased proportion of working women and nuclear families with less time available for cooking meals are some of the factors responsible.

JUNCS food - negative effects

Consumption of unhealthy foods by the younger generation of the country can lead to a public health crises. Adverse effects from consumption of JUNCS in children and adolescents are given in Table I.

Steps to reduce consumption of JUNCS

Strict legislative measures banning sale of JUNCS food near the schools should be implemented.

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Table I. JUNCS - Adverse effects

Adverse effects	Causes
Suboptimal nutrition[4]	Increased dietary content of carbohydrates, free sugars, total fats, saturated fats and sodium. Decreased dietary content of protein, fiber, potassium, minerals and vitamins
Overweight / Obesity	Nutritionally imbalanced diet often leads to rapid weight gain and obesity.
Cardiometabolic risk[5]	There is a strong association between ultra-processed diet and cardiometabolic alteration
Microbial contamination	Poor food hygiene during preparation and handling leads to gastrointestinal infections such as diarrhea, typhoid and hepatitis
Behavioral symptoms[6] • Hyperactivity-inattention disorders • Conduct / oppositional disorders	Unhealthy diets affect mental state and brain function through oxidative stress processes, inflammation and stress response systems
Dental caries	High sugar content of junk foods and drinks promotes dental caries.
Risk of cancers	Some of the additives used in ultra-processed foods such as nitrosamines and various substances formed during food preparations such as smoking (polycyclic aromatic hydrocarbons) and barbecuing (heterocyclic amines) may increase the risk of cancer,
Allergies	Some food additives and coloring agents such as tartazine, monosodium glutmate (MSG) and annatto can cause allergies.
Cardiac arrhythmias	Caffeinated drinks cause increase in the heart rate and predispose to arrhythmias

Box 2. IAP nutrition chapter consensus guidelines on JUNCS

- Avoid JUNCS in all children and adolescents as far as possible
- Limit consumption of JUNCS at home/outside to not more than once per week
- Do not mix meals and TV viewing.
- Freshly cooked home foods with minimal usage of free sugar and trans fat to be preferred over restaurant / packaged foods.
- Only healthy food should be included in lunch boxes taken to school.
- Never give JUNCS food as reward/gift to children as it may amount to promoting these unhealthy foods indirectly.
- Regional and seasonal whole fruits to be preferred over fruit juices in children and adolescents.
- No fruit juices/fruit drinks/sugar-sweetened beverage (SSBs) should be given to infants and young children aged below 2 years.
- For 2-18 years, fruit juices, fruit drinks and SSBs should be avoided as far as possible.
- Water should be encouraged as the best drink and should be promoted over fruit juices/drinks at home and school.
- Fruit juices/drinks, if given, should be limited to 125 mL per day for children aged between 2-5 years, and 250 mL per day for age >5 years; and these should preferably be given as fresh juices.
- Caffeinated drinks should not be consumed by children and adolescents.
- Carbonated drinks, tea and coffee to be strictly avoided in children less than 5 years.
- In 5-9 years, limit tea/coffee- to a maximum of 100 mL/day and in 10-18 years- limit to a maximum of 200 mL/day (provided no other caffeinated products are taken).

School canteen menus should only offer healthy food options. Availability of fruits and vegetables in the school canteens instead of JUNCS will promote healthy dietary habits. Similarly replacing sugar sweetened beverages with drinking water will also help to reduce consumption of the former. Stringent labeling laws should be enforced so that consumers can make healthier choices at the point of purchase. 'Traffic light labelling' for packaged food products, based on their fat, sugar and salt content with red for unhealthy products, amber for moderately healthy products and green for healthy products as suggested by food safety and standards authority of India (FSSAI) is a viable option. It is imperative to regulate the advertisements of fast foods and nonalcoholic beverages in TV, print media and social media. The practice of giving free toys/gifts with JUNCS foods should be banned. Higher taxes should be levied on unhealthy foods to discourage their consumption. School and community based educational programs should be conducted to create awareness among the children and parents regarding the adverse effects of JUNCS and the importance of curbing their use. Parents should themselves be good role models for children by adopting healthy eating habits.

The IAP Nutrition Chapter has released valuable consensus guidelines on reducing consumption of JUNCS for children and families (Box 2).[2]

The huge burden of non-communicable diseases among the adult population may have its origin in the dietary habits inculcated in childhood. School based health education and intervention programs can improve the dietary habits of children. Parents and the general public should also be sensitized to the ill effects of JUNCS consumption.

Points to Remember

- ***"JUNCS" should be avoided to the extent possible in all children and adolescents.***
- ***Packaged fruit juices /fruit drinks/sugar sweetened beverages are not to be given to children less than 2 years age, and to be avoided as far as possible in older children.***
- ***No caffeinated drinks are to be given to children and adolescents.***
- ***There must be strict regulations to control advertisements promoting consumption of "JUNCS" in TV, print and social media.***

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CLIPPINGS

WHO COVID-19 VARIANTS (04 December 2021)

Variant of interest and variant of concern

A variant is considered a variant of interest if it has mutations that are suspected or known to cause significant changes, and is circulating widely (e.g., known to cause many clusters of infected people, or found in many countries).

A variant of interest becomes a variant of concern if it is known to spread more easily, cause more severe disease, escape the body's immune response, change clinical presentation, or decrease effectiveness of known tools - such as public health measures, diagnostics, treatments and vaccines.

IAP - IJPP CME 2021

COMPUTERIZED TOMOGRAPHY HEAD IN PEDIATRIC EMERGENCIES

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*****Anitha Jasper**
*****Gibikote Sridhar**
******Debasis Das Adhikari**

Abstract: *Computerized tomography of the brain has often been used as an initial imaging modality in the assessment of children with neurological emergencies. It is readily available in most centers and it is less expensive. The disadvantages of computerized tomography are radiation exposure and a limited diagnostic value in the evaluation of certain conditions such as early stroke, demyelinating disorders, neurometabolic disorders, infection and tumors. However, skull fractures, calcification and intracranial bleed may be readily diagnosed on computerized tomography head. Computerized tomography plays a vital role in the initial evaluation of accidental and non-accidental brain injury, hydrocephalus, and intracranial space occupying lesion. Brain magnetic resonance imaging is the preferred diagnostic modality in the evaluation of neurological disorders. However, it is expensive, time consuming and poses logistic difficulties in an emergent scenario.*

Keywords: *Computerized tomography, Pediatric emergency, Neuroimaging.*

Neuroimaging forms an extended part of assessment in children presenting with neurological emergencies to the pediatric emergency department (PED). Neuroimaging often complements a meticulous history and neurological assessment in sick children and helps to diagnose intracranial pathologies.[1] Neurological emergencies in children could result from traumatic brain injury, acute meningoencephalitis, tumor, stroke, hypoxic ischemic encephalopathy, inborn errors of metabolism and non-accidental head trauma.[2] The physician in the PED has to decide on the need for neuroimaging and also choose the preferred modality of neuroimaging in any given patient. Though magnetic resonance imaging (MRI) brain is the ideal modality of neuroimaging in most of the above discussed neurological emergencies, considering the lack of availability in resource limited settings, need for sedation and longer time to acquire the images and affordability issues, computerized tomography (CT) of brain is often chosen in pediatric emergencies. An emergent CT brain may be useful to diagnose skull fractures, intracranial bleed, intracranial space occupying lesions and calcification.[2] However, the limitations encountered with regard to CT brain are exposure to radiation and limited diagnostic yield in patients with early stroke, white matter lesions, inflammation, infection, neurometabolic disorders and brainstem pathologies. In this review, the utility, radiological findings and limitations of CT brain in pediatric neurological emergencies will be briefly discussed.

Technical aspects of CT

The technique of CT was developed by Sir Godfrey Hounsfield in 1972. Clinicians must understand the basic physics and technical aspects of CT. While acquiring CT brain images, a patient is placed under moving X-rays on a gantry and the radiation is absorbed or attenuated variably depending on the density of tissues in the head. The absorbed or attenuated radiation is detected by a computer and the images are generated.[1] A pixel refers to the basic building block of a computer image while a voxel denotes a three-dimensional pixel. The number assigned by the computer to each voxel corresponding to the attenuation by tissues represents the Hounsfield unit (HU). Air has less absorption and allows most of the radiation to reach the detector resulting in low attenuation which is displayed dark (hypodense). Bone absorbs maximum radiation and allows only a small amount of radiation to

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Table I. Various tissue types with their corresponding Hounsfield units and their appearance on CT

Tissue	Appearance on CT
Air (-1500HU)	Black
Fluid (0-10HU)	Dark
Acute blood (60-70HU)	White
Chronic blood (30-40HU)	Dark grey
Bone (>350HU)	Bright white

reach the detector resulting in high attenuation which is displayed bright (hyperdense). The water density is centered at zero. The ranges of HU that correspond to the various tissues and their appearance on CT are depicted in Table I.[1]

The first-generation CT machines acquire only a single image in one rotation of gantry while the recently used multislice CT machines acquires 64 images in a single rotation, thereby reducing the image acquisition time and also improves the spatial resolution. The axial, coronal and sagittal images may be reconstructed. The process of setting a range of HU on the computer screen to visualize the different tissues such as bone or soft tissue is called as windowing. The advantages and disadvantages of CT head are summarized in Table II.

Table II. Advantages and disadvantages of CT head

Advantages	Disadvantages
• Ease of availability	• Exposure to ionizing radiation
• Lesser cost compared to MRI	• Early changes in stroke may be missed
	• Limited resolution in patients with white matter lesions, infection, inflammation, neurometabolic disorders and tumors
• Shorter imaging time	
• Lesser need for sedation	
• No contraindications in patients with metallic implants	
• Good resolution in skull fractures, calcification and bleed	

Patient preparation for acquisition of CT head

The adequate preparation of a child for acquisition of CT head is equally important as an optimal CT technique. The prerequisites to be addressed in a sick child undergoing CT head includes:[3]

- Psychological preparation of patient and parents
- Assessment of the need for sedation in children lesser than 5 years old or children with neurodevelopmental disorders
- Assessment of the hemodynamic status and stabilization of airway before transferring for neuroimaging
- Assessment of the need for intravenous contrast and dosage
- Record any allergies in the past to medications or contrast

The preparation for neuroimaging in an emergency setting starts with the counseling of parents about the scanning environment, safety, cost and utility. Older children must also be counseled regarding the safety of scanning environment and nature of the procedure to reduce anxiety and stress. In children younger than five years of age, children with neurodevelopmental disorders and children with altered mental status, sedation may be required to obtain the images. Parents must be allowed to stay with the children during the acquisition of images. A good intravenous access must be established in children with a need for contrast enhanced images. The intravenous contrast material must be injected using a power injector rather than manual intravenous push. The technical parameters must be tailored to the age of the child and the part of the body to be imaged to achieve a good diagnostic image quality.

Research data from atomic bomb survivors demonstrate that children are more vulnerable than adults to the effects of ionizing radiation especially in the development of leukemia. Children have longer life expectancy from the time of exposure which provides enough time for a cancer to manifest. Radiation effects are more likely to occur in proliferating cells and as growing children have more proliferating cells, more prone for radiation damage.[4]

Children face an increased risk from CT radiation due to larger doses and increased lifetime radiation exposure with an estimated 0.07% mortality risk from brain tumors as reported in literature. The increased dose per milliampere-second and the increased lifetime risk per unit dose are attributable factors.[5]

A documented positive association between CT radiation dose and development of leukemia and brain tumours has been established. Doses of about 50 milliGray (mGy) increases the risk of a leukemia three fold and 60mGy triples the risk of brain cancer. Though the benefits of CT outweigh the risks, it is imperative to reduce the dosage of radiation as much as possible.[6]

Care must be taken to avoid exposure of ionizing radiation to radiosensitive organs. Precaution to minimize radiation exposure include proper application of radiation protection shields, dose reduction, dosage monitoring in compliance with the "as low as reasonably achievable "(ALARA principle) and use of nonionic contrast agents.[7]

CT head findings in various intracranial pathologies

Traumatic brain injury (TBI)

TBI is one of the major causes of mortality and morbidity in children from both developing and developed countries. CT head remains the preferred diagnostic imaging modality in children presenting with TBI as the image acquisition is rapid and it provides relevant information about primary and secondary brain injuries. Though CT head can reliably detect skull fractures and intracranial bleed, it is not very sensitive to detect diffuse axonal injuries, early infarcts, small extradural and subdural hemorrhages, brainstem injuries and timing of the bleed. Based on the Glasgow coma scale, the severity of TBI may be categorized into mild (GCS 13-15), moderate (GCS 9-12) and severe (GCS 3-8). American Academy of Neurology does not recommend the use of CT brain in children with sports related trauma but its use must be tailored to patients with severe TBI manifesting with altered mental status, drop in GCS, focal neurological deficits, post-traumatic amnesia, suspected skull fracture or signs of neurological deterioration.[8] Skull fractures may occur following accidental or abusive head trauma. Calvarial fractures are asymmetric, unilateral, extend beyond sutural lines with poorly demarcated non-sclerotic borders and are often associated with adjacent soft tissue swelling. Bilateral fractures are also asymmetric and may be displaced or comminuted.[2] CT head with three-dimensional reconstruction may be better in detecting transverse fractures. Fig.1A and 1B shows an occipital depressed fracture in a child following trauma.

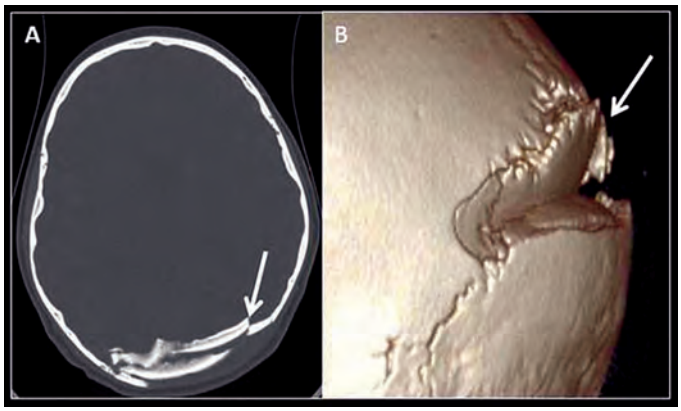

Fig.1.Plain CT in the bone window (A) and 3D reconstructed volume rendered images (B) shows an occipital depressed fracture (white arrows) in a ten-year-old boy with history of trauma

Epidural hematoma results from disruption of the middle meningeal artery or a dural venous sinus. It manifests as biconvex hyperdense extra-axial collections between the dura and inner table of skull. They are commonly associated with fractures and do not extend

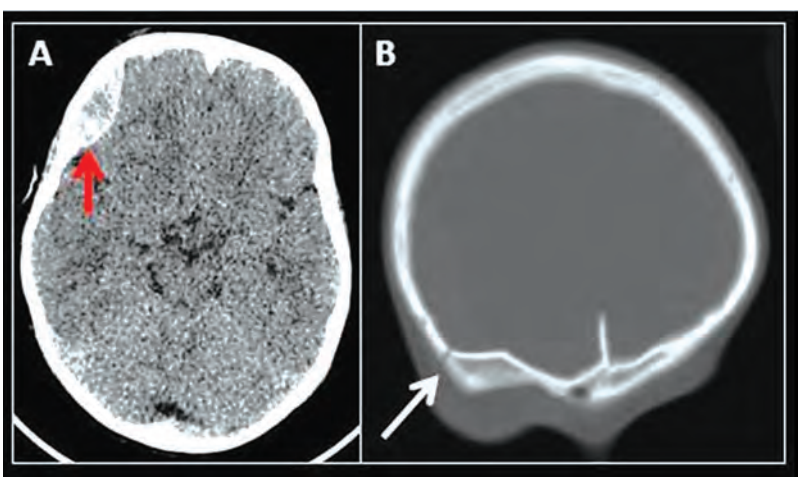

Fig.2. Plain CT shows an acute epidural hematoma in the right frontal region (red arrow in A) with an underlying fracture (white arrow in B) in a four-year-old boy with history of trauma

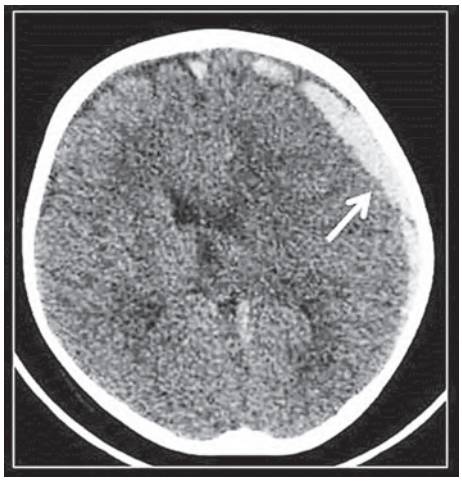

Fig.3. Plain CT shows a crescentic subdural hematoma (white arrow) along the left fronto-parietal convexity with mass effect on the underlying parenchyma in a two-year-old boy with history of trauma

beyond suture lines. The characteristic "swirl sign" indicating active hemorrhage, is due to areas of hypodensity within the hyperdense extradural hemorrhage (EDH) making it appear heterogenous.[9,10] Fig.2A and 2B shows an epidural hematoma in the right frontal region with an underlying fracture. Subdural hematoma results from rapid accelerating and decelerating forces during high velocity motor vehicle collisions and falls from height causing rupture of the bridging veins. CT shows hyperdense crescentic collection of blood in the subdural space. Subdural hematoma is frequently seen in non-accidental injury.[9] There may be associated mass effect, cerebral edema, midline shift and herniation thereby increasing the risk of subsequent mortality.[10] Fig.3 shows crescentic subdural hematoma along the left fronto-parietal convexity with mass effect. Subarachnoid hemorrhage is due to tearing of subarachnoid vessels or extension of adjoining parenchymal hematomas into the subarachnoid space. They curvilinearly trace the sulci and cisternal spaces and appear hyperdense on CT.[9] Fig.4 shows extensive subarachnoid hemorrhage along the basal cisterns. Intraventricular hemorrhage occurs due to subependymal or choroid plexus bleed or extension of adjacent subarachnoid or parenchymal bleed and appear hyperdense on CT head. When associated with obstructive hydrocephalus,they pose a greater threat of neurological complications and mortality in children.[9] Fig.5A and 5B

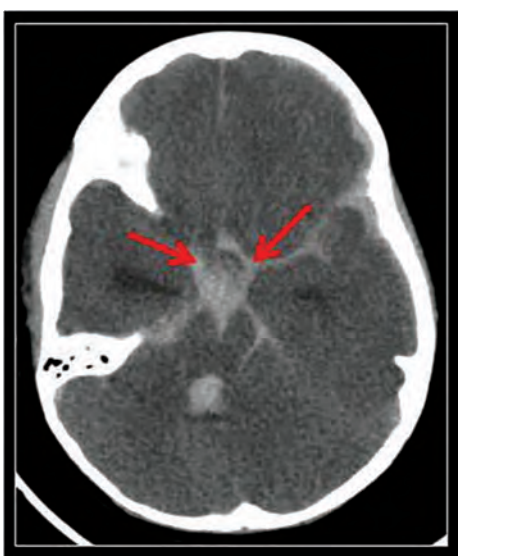

Fig.4. Plain CT shows extensive subarachnoid hemorrhage along the basal cisterns (red arrows) in a three-year-old child with status epilepticus

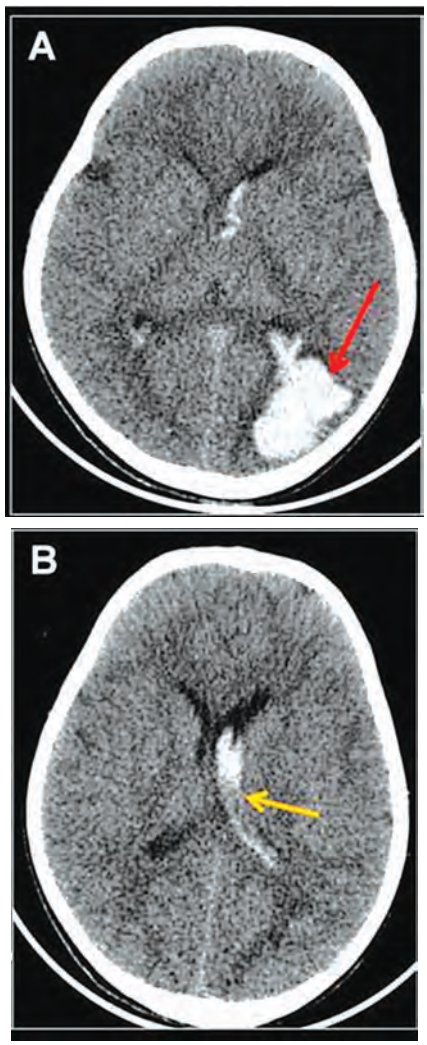

Fig.5. CT brain shows a left parietal hematoma (red arrow in A) with intraventricular extension (yellow arrow in B) due to an underlying arterio-venous malformation in a ten-year-old child

shows a left parietal hematoma with intraventricular extension. Cerebral contusion results from coup and contrecoup injuries causing hemorrhages of the cerebral gray matter vasculature that may involve the white matter occasionally. Non-contrast CT shows wedge shaped hyperdense lesions commonly involving the gyri of inferior frontal and anterior temporal lobes.[10] Fig.6A and 6B shows parenchymal contusion in left frontal lobe with fracture of the overlying bone. Intraparenchymal hematoma arises due to hemorrhage of the brain vasculature. The "swirl sign" in plain CT and "spot sign" in CT angiography are indicative of an expanding hematoma due to fresh bleeding within the existing lesion triggered by local edema and ischemic changes.[9] Children have restricted intracranial space when compared to adults and are more prone to

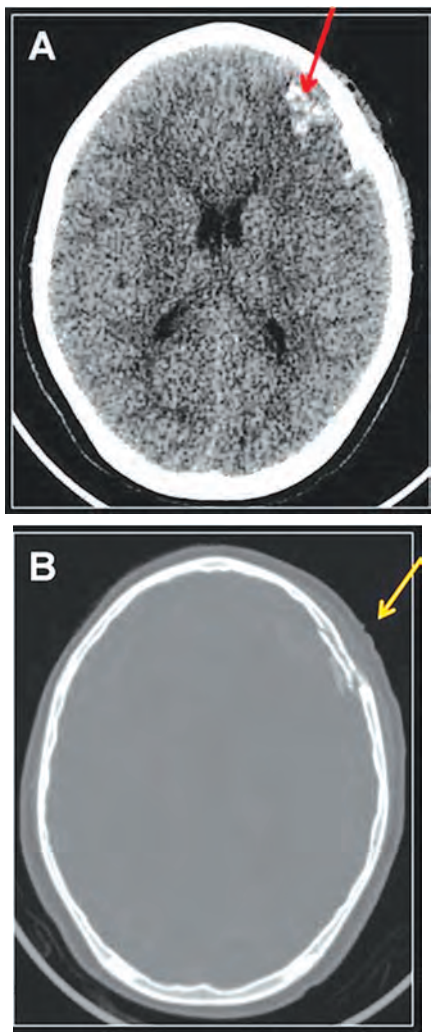

Fig.6. Plain CT showing a parenchymal contusion (red arrow in A) in the left frontal lobe. CT sections in bone window shows a fracture of the overlying bone (yellow arrow in B) in a thirteen-year-old child with history of fall from height

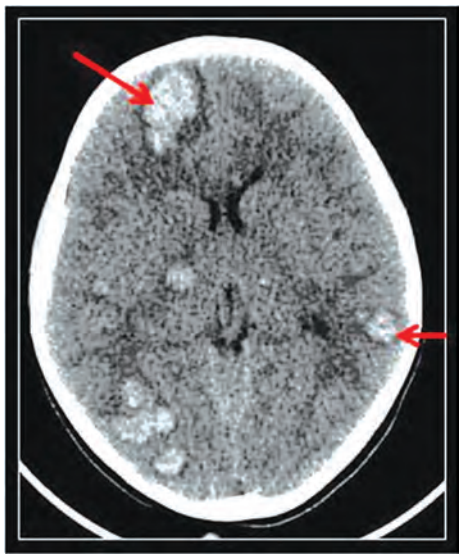

Fig.7. CT brain plain shows with multiple intraparenchymal hematomas (red arrows) in a five-year-old child

subsequent neurological complications arising due to the effects of ischemic damage and raised intracranial tension.[9] Fig.7 shows multiple intraparenchymal hematomas on a plain CT brain.

Diffuse axonal injury (DAI) is a consequence of sudden rotational acceleration-deceleration from high velocity automobile accidents causing shearing and axonal stretching. Gray-white matter junction, corpus callosum, internal capsule, midbrain, brainstem, basal ganglia and thalamus are susceptible to axonal shear injury.[9] DAI causes more significant impairment compared to hematomas and contusions. There may be a discrepancy between clinical status and initial imaging findings which may be normal or only minimally abnormal.[11] Initial imaging modality remains CT, though MRI is more sensitive and diagnostic for DAI. CT may identify either hyperdense hemorrhagic DAI or hypodense lesions of non-hemorrhagic DAI. Presence of microhemorrhages and edema in MRI indicates severity and worse prognosis.[10]

Herniation results from parenchymal edema causing a mass effect on surrounding structures. The brain parenchyma is displaced between compartments manifesting as cranial nerve palsies, hemiparesis and fatal raised intracranial pressure. Fig.8 and Fig.9A-C depict the various types of intracranial hemorrhage and brain herniation syndromes. Subfalcine herniation is midline shift when anterior cingulate gyrus is displaced underneath the falx cerebri. Fig.10 shows a subfalcine herniation caused by a large left parieto-occipital mass. Descending transtentorial herniation (DTH) occurs through the tentorial

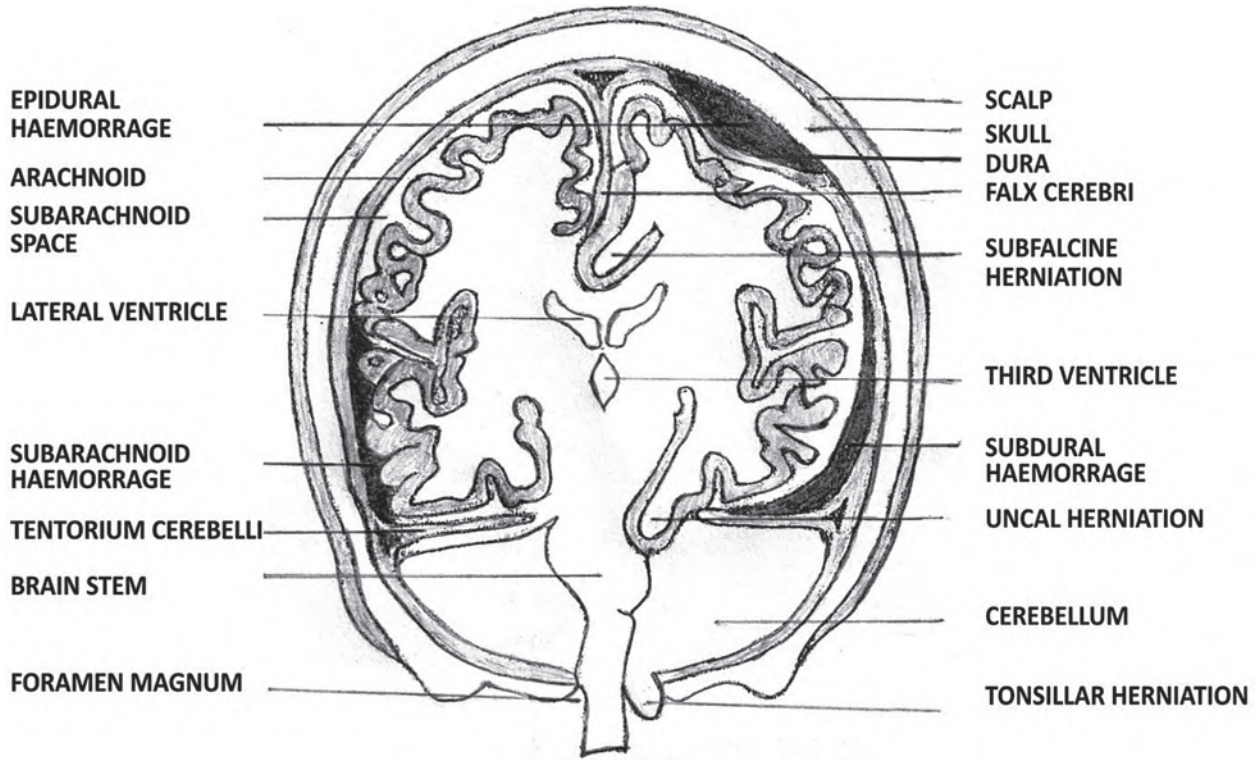

Fig.8. A diagrammatic representation of intracranial hemorrhages and herniations

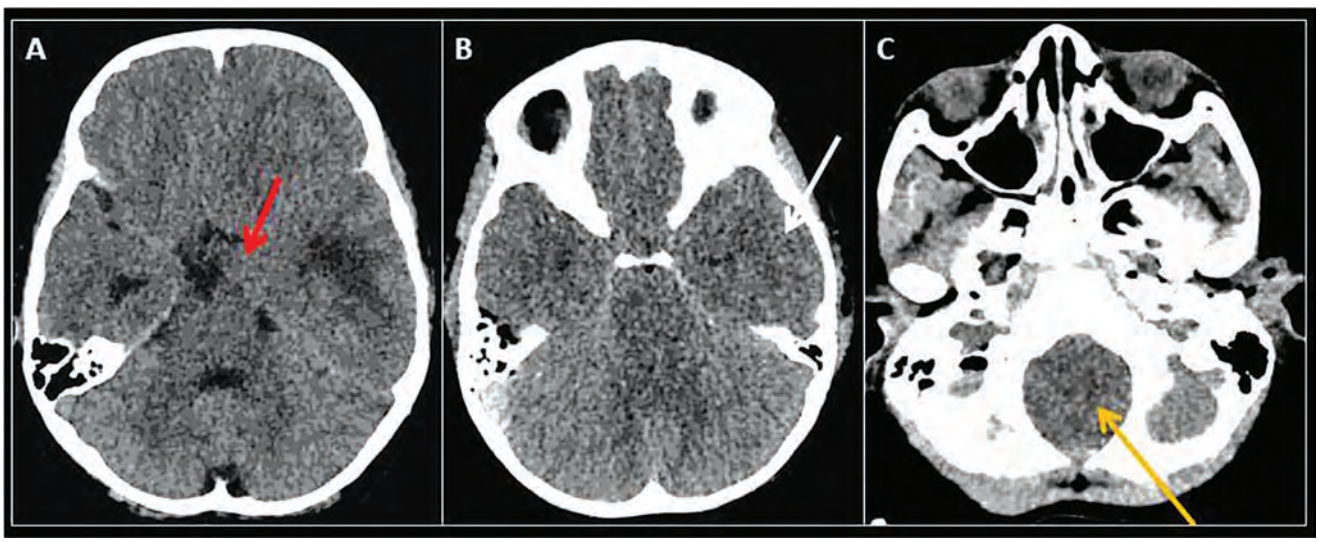

Fig.9A-C. CT brain plain shows left sided uncal herniation (red arrow in A), cerebral edema with loss of grey-white differentiation and sulcal effacement (white arrow in B) and tonsillar herniation (yellow arrow in C) in a six-year-old child with history of trauma

incisura. Axial CT in unilateral (uncal) DTH reveal medial uncal displacement and effaced suprasellar cistern. Progression of DTH shows hippocampal herniation and displacing midbrain against the contralateral cerebral peduncle (Kernohan's notch). In patients with tonsillar herniation, the cerebellar tonsils are displaced inferiorly and get impacted in the foramen magnum. CT shows herniation of tonsils into foramen magnum obliterating the cisterna magna. In ascending transtentorial herniation, the cerebellar vermis and hemispheres are pushed upward through the tentorial incisura due to an expanding posterior fossa mass resulting in obstructive hydrocephalus. CT shows effacement of CSF in superior vermian cistern and midbrain compression.[10]

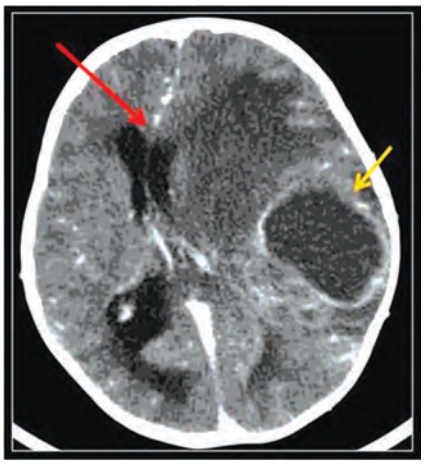

Fig.10. Contrast enhanced CT brain shows a large left parieto-occipital mass (yellow arrow) causing subfalcine herniation (red arrow) in a seven-year-old child

Non-accidental injury (NAI)

Initial imaging of suspected child abuse should include a complete skeletal survey and plain CT brain. Plain CT brain helps to detect fractures and intracranial bleed.[12] Non accidental injury is the major cause of subdural bleed in infants.[13] Acute subdural hematomas appear hyperdense and older hematomas appear hypodense. Brain MRI is recommended to identify older hematomas of differing ages. Contusions, shear injuries and cerebral edema are also seen. Isolated interhemispheric subdural hemorrhage (SDH), bilateral hemorrhages, hematomas of varying ages, complex multiple fractures or concomitant retinal hemorrhages are suspicious of NAI.[2,14]

Neuroinfection

Meningitis may be either pachymeningitis involving the dura and arachnoid or leptomeningitis involving the pia and arachnoid. Various infections including bacterial, viral, tuberculosis and fungal can cause infectious meningitis. Noninfectious meningitis may be inflammatory, carcinomatous, chemical or reactive.[15] Normal vascular enhancement is thin, smooth, discontinuous and symmetric involving the parasagittal areas, sparing the sulci and may be seen even in the absence of a pathology but abnormal pathological enhancement is thick, nodular, continuous, asymmetric and extends typically into the sulcal base. Infectious meningitis causes leptomeningeal enhancement. Pachymeningeal enhancements mostly occur in non-infectious meningitis. Thin and linear pattern is observed in bacterial and viral infections whereas thick and nodular enhancement is seen in fungal infections. Acute meningitis involves cerebral convexities and chronic meningitis involves basal cisterns.[2] The meningeal layers and spaces are depicted in Fig.11.

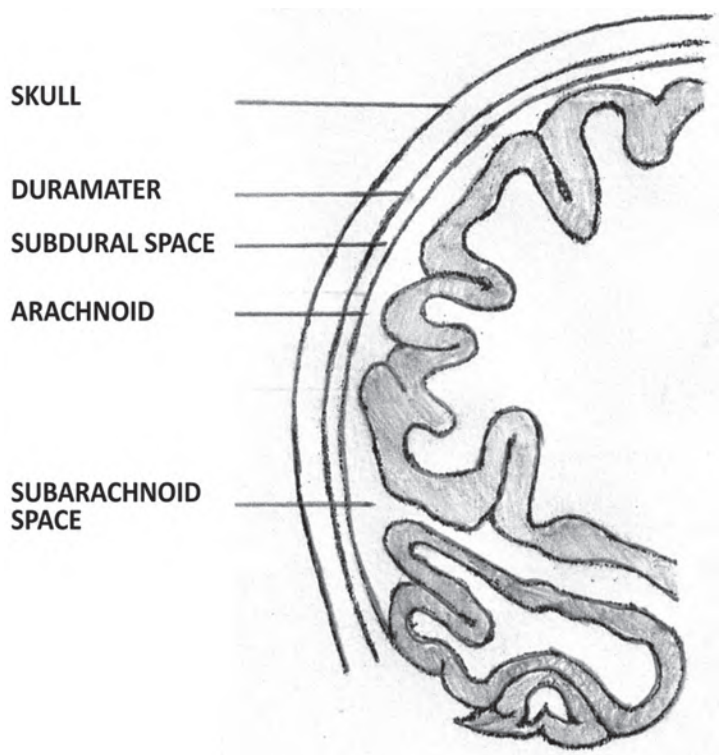

Fig.11. Coronal section through the brain showing the meningeal layers and spaces

In acute pyogenic meningitis, enhancement in neuroimaging is non-specific and the mainstay of diagnosis remains clinical with cerebrospinal fluid cultures. In acute pyogenic meningitis, an initial neuroimaging may not reveal any abnormalities. MRI including diffusion weighted imaging (DWI), fluid attenuated inversion recovery (FLAIR) and post contrast imaging is more sensitive in detecting empyema, basal cistern enhancement, sulcal enhancement and infarcts but CT is valuable in an emergency to rule out raised intracranial pressure prior to lumbar puncture and to detect life threatening complications such as cerebral edema and hydrocephalus.[16] Cranial CT detects communicating and non-communicating hydrocephalus. It aids in timely neurosurgical shunt placement to prevent catastrophic brain herniation and morbid neurological sequelae. Subdural effusions are isodense to CSF and crescent shaped. Subdural empyema is also crescentic but can have peripheral enhancement. The location and type of extra-axial fluid collection determines surgical drainage. Early cerebritis appears as focal and poorly demarcated hypodense lesions on CT with absent contrast enhancement.[16] Early abscess detected by a timely contrast enhanced computerized tomography (CECT) shows incomplete ring enhancement when the infection is still amenable to antibiotic therapy. An abscess detected in its later stages shows complete ring enhancement. CECT brain showing a left parietal lobe abscess with peripheral ring enhancement and perilesional edema causing mass effect and midline shift is depicted in Fig.12. Ventriculitis is detected by CT which shows enhancement of the ventricular walls, ventricular dilatation, intraventricular debris and septations. Undetected ventriculitis can prove fatal if not promptly intervened by surgical shunting procedures.[16]

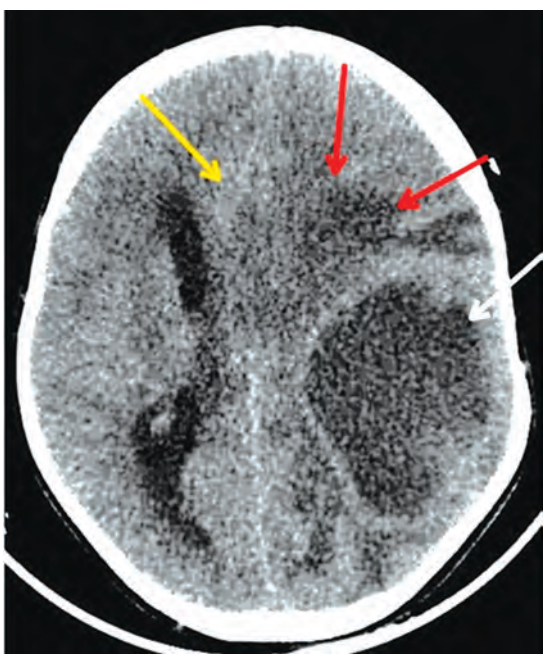

Fig.12. 5 year old girl with Tetralogy of Fallot and fever for 5 days. Contrast enhanced CT shows a large left parietal lobe abscess with peripheral rim enhancement (white arrow) and marked perilesional edema (red arrows) causing mass effect on the left lateral ventricle and midline shift (yellow arrow)

The imaging finding in viral encephalitis are summarized below:[17]

- Herpes simplex virus type 1 encephalitis- hypodense lesions in temporal lobe.
- Herpes simplex virus type 2 encephalitis- diffuse white matter hypodensities.
- Varicella encephalitis - multifocal hypodense deep white matter lesions with cerebral edema with or without contrast enhancement.
- Arboviral encephalitis-hypodense lesions in thalamus, basal ganglia, brainstem and deep white matter.
- Enteroviral encephalitis-multiple white matter hypodensities.

Hypoattentution in basal ganglia, subcortical and periventricular white matter is seen in early subacute sclerosing panencephalitis with wide spread atrophy of the cortex in late stages.[17]

Tuberculous meningitis (TBM) has a striking predilection for basal cisterns.[17] Contrast enhanced MRI is more sensitive compared to contrast enhanced CT in detecting abnormal meningeal enhancement of the basal cisterns.[16] CT and MRI brain in TBM show hydrocephalus and basal cistern enhancement.[17] With disease progression, thick exudates entrapping vessels and nerves result in infarcts and cranial nerve palsies. Contrast enhanced CT shows intense leptomeningeal enhancement. CT findings of a tubercular abscess are similar to a pyogenic abscess with ring enhancement and mass effect. Tuberculomas are space occupying lesions mainly involving the cerebral hemispheres, cerebellum and basal ganglia. They may be solitary or multiple isodense lesions with ring enhancement on CECT.[17] CECT brain with multiple tuberculomas, communicating hydrocephalus and chronic infarct in left basal ganglia is shown in Fig.13A and 13B.

MRI is the better imaging modality for depicting neurocysticercosis. In the vesicular stage, CT shows non-enhancing thin walled cyst. In colloid stage, CT shows ring

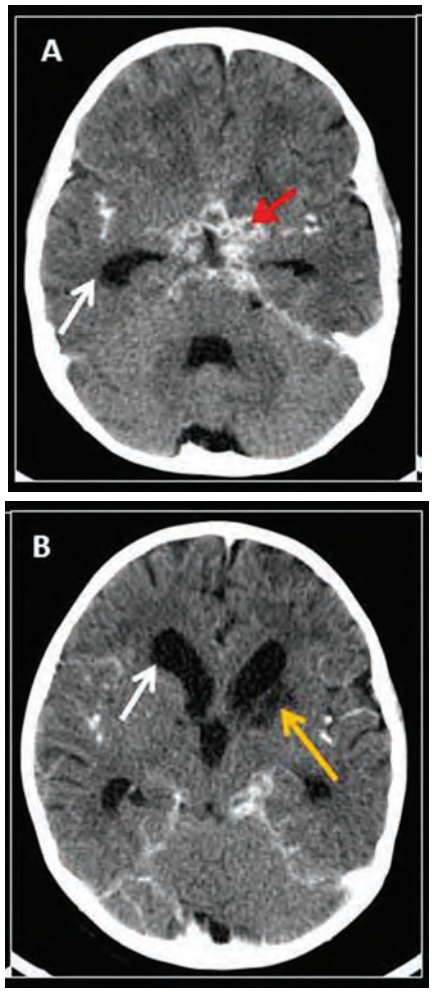

Fig.13. CECT brain shows multiple tuberculomas in the basal cisterns (red arrow in A), communicating hydrocephalus (white arrows in A and B) and a chronic infarct in the left basal ganglia (yellow arrow in B) in a six-year-old boy with tuberculous meningitis

enhancing lesion. In the involution stage, there is ring enhancement and the lesion is similar to tuberculoma or an abscess. Calcification without contrast enhancement is seen in chronic lesions.[17] The salient differences between tuberculoma and neurocysticercosis on CT brain are summarized in Table III.[18]

Fungal infections occur in both immunocompetent and immunocompromised children. Brain CT findings in histoplasmosis and aspergillosis show evidence of leptomeningitis, cerebritis, infarcts and abscess. CT in cryptococcal infections reveal hydrocephalus, meningeal enhancement and ring enhancing nodules.[17] Cranial CT findings in congenital infections such as congenital toxoplasmosis reveal hydrocephalus, brain atrophy, infarcts and subependymal, basal ganglia or diffuse calcification.[17] Diffuse cerebral atrophy and punctuate calcifications in

Table III. Key differentiating features between tuberculoma and neurocysticerscosis on CT brain

Tuberculoma	Neurocysticercosis
Irregular margins	Round, smooth regular margins
Size >20 mm	Size <20 mm
Severe mass effect common	Severe mass effect rare

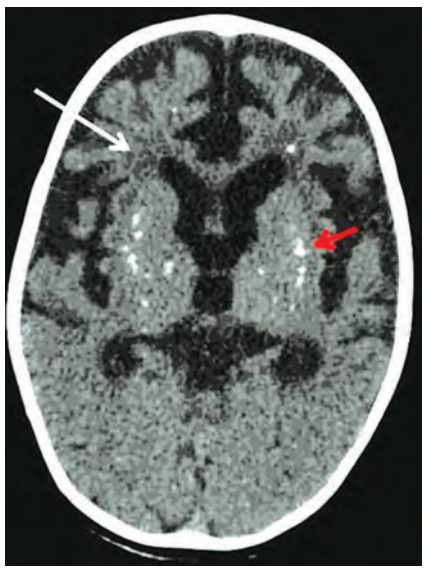

Fig.14. Plain CT brain shows diffuse cerebral atrophy, more marked in the frontal regions with hypodensity of the white matter (white arrow) and punctate calcification in the periventricular regions and basal ganglia (red arrow) in a one-year-old child with suspected TORCH infection

the periventricular regions and basal ganglia in a child with suspected TORCH infection is shown in Fig.14. Rubella causes widespread cystic changes and temporal lobe calcification. Early congenital Herpes simplex virus (Type 2) infection cause focal or global cerebral white matter hypoattentuation. Calcification and cystic encephalomalacia may occur over time.[17]

Hydrocephalus

Blockage of cerebrospinal fluid at any site between choroid plexus and arachnoid villi results in hydrocephalus. Obstruction at level of foramen of Monro, aqueduct of sylvius or foramen of Luschka and Magendie results in non-communicating hydrocephalus.[19] CT in a child with communicating hydrocephalus demonstrates symmetric dilatation of lateral, third and fourth ventricles. Obstructive hydrocephalus due to medulloblastoma and

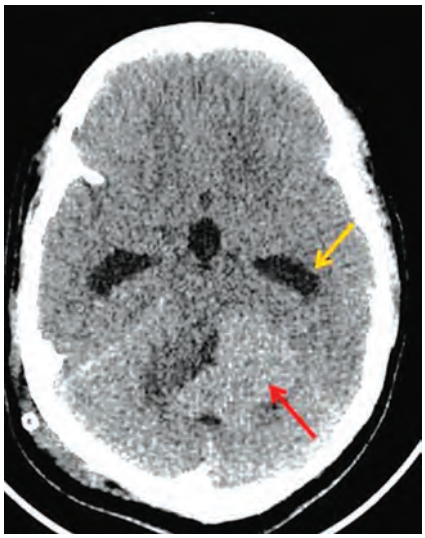

Fig.15. Plain CT brain showed a large hyperdense mass (medulloblastoma) in the left cerebellar hemisphere and vermis (red arrow) causing mass effect on the fourth ventricle with moderate obstructive hydrocephalus (yellow arrow) in a twelve-year-old girl with history of giddiness

craniopharyngioma on CT are shown in Fig.15 and Fig.16A and 16B. In non-communicating hydrocephalus, CT shows ventricular dilatation proximal to site of obstruction.[20] Ventriculomegaly associated with periventricular hypoattenuation on plain CT indicates interstitial edema warranting urgent need for neurosurgical intervention.[19] Children with shunted hydrocephalus may have complications due to shunt infection or malfunction. In infected shunts, imaging is of less value and CSF cultures are diagnostic. Shunt survey is done with X-rays of cranium, thorax and abdominal regions. The length of shunt, identification of breaks, kinks, migration, disconnection and pseudocyst formation are assessed.[2] CT is preferred over MRI to localize catheter tip. However, MRI offers better advantage over CT by reducing risk of radiation exposure and provides better detail on ventricular size, cause of hydrocephalus and evaluating endoscopic third ventriculostomy patency.[21]

Pediatric stroke

Stroke in children can result from hemorrhage or ischemia. Children with congenital heart defects, prothrombotic states, sickle cell disease, sepsis, trauma and malignancies are at risk for arterial ischemic stroke.[22] MRI brain with diffusion weighted images and magnetic resonance angiography is the imaging of choice. CT has limitations since it cannot distinguish infarct from meningoencephalitis and other mimics, has suboptimal demonstration of acute infarcts as well as carries the risk of radiation. Despite these drawbacks, CT is invaluable in an emergent scenario to give a prompt diagnosis when MRI is unavailable or the child is hemodynamically unstable for an MRI. Non-contrast CT findings in patients with stroke include "hyperdense artery sign" denoting thrombus in the vessel, loss of grey-white matter interface and perilesional edema.[22] Acute infarcts in the left capsuloganglionic region are depicted in Fig.17 and infarcts in the right anterior and middle cerebral artery and hyperdense middle cerebral artery sign are shown in Fig.18A and 18B. Non-contrast CT excludes an acute bleed and facilitates the decision to initiate thrombolytic therapy.

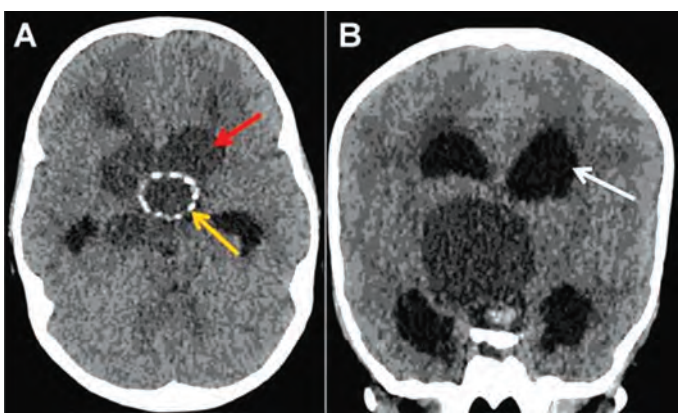

Fig.16. CT brain plain shows a large suprasellar predominantly cystic craniopharyngioma (red arrow in A) and foci of calcification within the lesion (yellow arrow in A) with features of obstructive hydrocephalus (white arrow in B)

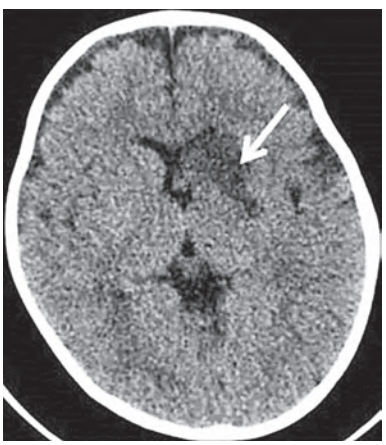

Fig.17. Plain CT brain shows an acute infarct in the left basal ganglia (white arrow), involving the left lateral lenticulostriate territory in an one-year-old girl with history of acute onset right sided weakness and right facial palsy

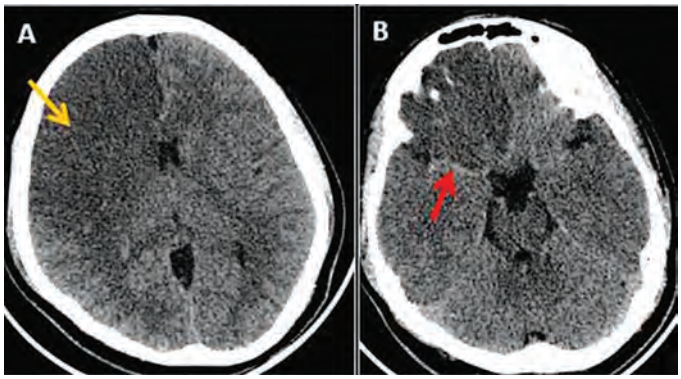

Fig.18. Plain CT brain shows a large area of hypodensity involving the right anterior and middle cerebral artery territories (yellow arrow in A) with hyperdensity of the right MCA (red arrow in B), suggestive of acute infarcts with thrombosis of the right MCA.

Hemorrhagic stroke is caused by intracranial hemorrhage due to causes other than trauma such as arteriovenous malformation, cavernous angioma, aneurysms, thrombocytopenia, disseminated intravascular coagulopathy and malignancies.[22] MRI is the imaging procedure of choice because CT has limited ability to detect vascular malformations. Predisposing conditions for cerebral sinovenous thrombosis include infection, trauma, polycythemia and prothrombotic states.[22] Dural venous sinuses, superficial cortical veins and the deep venous system can be affected. Fronto-temporal lobes, the thalami and basal ganglia may show areas of hypodensity on CT. Non-contrast CT reveals "cord sign" due to hyperdensity of intravascular thrombus in the acute stage. While with progression, CECT or CT venogram shows "empty delta sign" where the contrast outlines a triangular filling defect, representing the hypodense thrombus within the sinus.[22] Plain CT depicted in Fig.19 (A-D) shows hyperdensity in the straight sinus, internal cerebral veins, superior sagittal sinus and in the left transverse sinus with hemorrhagic venous infarct in the left temporal lobe.

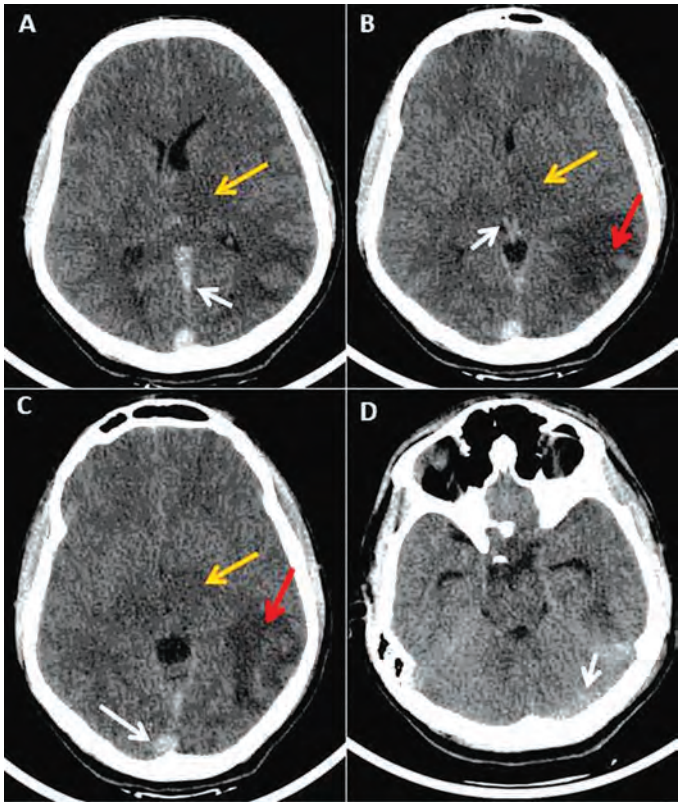

Fig.19. Plain CT brain shows hyperdensity in the straight sinus (white arrow in A), internal cerebral veins (white arrow in B), superior sagittal sinus (white arrow in C) and in the left transverse sinus (white arrow in D) with hemorrhagic venous infarct in the left temporal lobe (red arrows in B and C). Early infarcts in the thalami seen as ill-defined areas of hypodensity in the thalami, more severe on the left side (yellow arrows in A,B,C) in a sixteen-year-old boy with history of altered sensorium, drowsiness and loss of speech for four days with superficial and deep venous thrombosis

Cerebral venous thrombosis involving superior sagittal sinus, left transverse sinus, internal cerebral veins and straight sinus

Hypoxic ischemic encephalopathy (HIE)

HIE may occur following cardiac arrest, traumatic brain injury, status epilepticus, shock and infection. Watershed pattern is seen in mild to moderate hypoxic injury involving frontal and parietal lobes and ganglionic pattern seen in moderate to severe hypoxic injury affecting basal ganglia, thalami, hippocampal region and corticospinal tracts.[2] Hypoxic ischemia results in loss of grey-white matter differentiation due to edema. Non-contrast CT shows hypodensity in watershed zones of major vessels in mild to moderate HIE. In severe HIE, the deep grey nuclei show hypoattenuation. The midbrain and cerebellum are less affected, cerebrum appears hypodense compared to cerebellum resulting in "white cerebellum sign".[2] Non-contrast CT shows "reversal sign" which is inversion of the normal relative densities of gray and white matter with gray matter demonstrating lower attenuation than the white matter. Presence of reversal sign reflects risk of mortality and permanent neurological impairment.[23]

Posterior reversible encephalopathy syndrome (PRES)

PRES may occur in patients treated with cyclosporine, hypertension, autoimmune disease and infection. Non-contrast CT shows poorly demarcated hypodense lesions in subcortical white matter of parieto-occipital lobes, brainstem, basal ganglia and cerebellum.[2] Contrast enhancement is observed due to breakdown of blood brain barrier. The lesions usually resolve following therapy.[2] Symmetric hypodensities in subcortical white matter of the parieto-occipital lobes in a patient with PRES is shown in Fig.20A and 20B.

Status epilepticus

MRI brain is recommended for evaluation of seizures by the American Academy of Neurology (AAN) and International League Against Epilepsy (ILAE) but may not be readily available in all emergency departments.[24,25] Stabilization of the child takes precedence to neuroimaging.[26] In an emergency setting, non-contrast CT brain is invaluable in providing timely diagnosis and intervention of acute symptomatic seizures due to trauma, intracranial bleed, cerebral edema, brain herniation, hydrocephalus, calcification, abscess, CNS infections and neoplasms.[24]

Acute disseminated encephalomyelitis (ADEM)

ADEM is a monophasic immune-mediated demyelinating disorder which follows few weeks after vaccination or viral infection. In the presence of large lesions, non-contrast CT reveals focal hypoattenuating lesions in white matter or gray matter nuclei. MRI is the preferred imaging modality in the evaluation of children with suspected ADEM.[27]

Tumors

Supratentorial tumors predominate in infants. Subependymal giant cell astrocytoma associated with tuberous sclerosis are seen as heterogenous calcified lesions on a plain CT. Oligodendrogliomas appear as hypodense frontotemporal tumors. Dysembryo plastic neuro epithelial tumors are peripherally hypodense and minimally enhancing lesions on CT. CT brain in patients with pineoblastoma reveals a hyperdense lesion with exploded calcification in the periphery.[28] Fig.16A and 16B CT brain in a child with suprasellar craniopharyngioma reveals foci of calcification and obstructive hydrocephalus. Infratentorial tumors are commonly encountered in children above four years. CT brain in juvenile pilocytic astrocytoma shows a large cystic cerebellar lesion. The solid region of the tumor appears hypodense.[29] High grade gliomas are

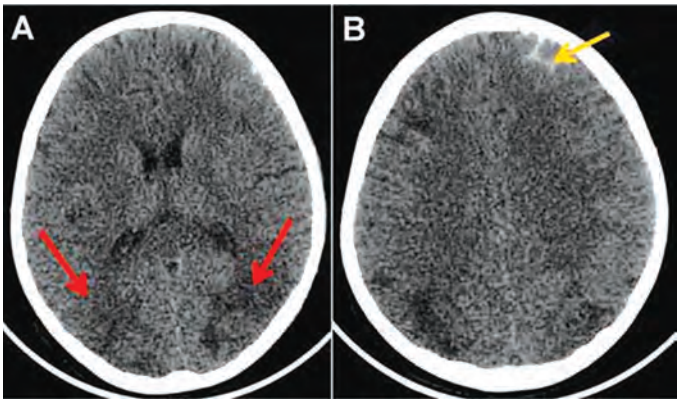

Fig.20. Plain CT brain shows symmetric hypodensities in the subcortical white matter of the parieto-occipital lobes (red arrows in A), suggestive of PRES. Hyperdensity along the sulcal space in the left anterior frontal region (yellow arrow in B), suggestive of subarachnoid haemorrhage in a twelve-year-old child with systemic lupus erythematosus and seizures

hyperdense. Medulloblastoma on plain CT appear as hyperdense or isodense midline lesions. Contrast CT shows diffuse enhancement. CT brain of a child with medulloblastoma shows mass effect on the fourth ventricle and obstructive hydrocephalus as shown in Fig.15. Ependymomas are seen as infratentorial hyperdense lesions in the fourth ventricle with calcification and contrast enhancement. Atypical teratoid or rhabdoid tumor which is an aggressive tumor, is seen as a heterogenous and hyperdense lesion with contrast enhancement. Hemangioblastomas appear as cystic lesions with a solid intensely enhancing component or solid intensely enhancing lesions on CT involving the posterior fossa. Schwannoma are extra-axial lesions appearing hypodense and show heterogenous contrast enhancement. Meningiomas are usually associated with neurofibromatosis type 2 and show calcification and hyperostosis of adjacent bone. Epidermoid cysts appear hypodense.[29]

Conclusion

Computed tomography is thus a valuable tool in the evaluation and management of acute pediatric neurological emergencies. The increased vulnerability of children to radiation hazard warrants judicious use of CT scans through use of evidence-based guidelines and alternate imaging modalities may help to avoid unnecessary radiation exposure.

Points to Remember

- ***CT is often readily available, less time consuming and less expensive.***
- ***An emergent CT head is useful in the diagnosis of skull fractures, intracranial bleed, space occupying lesions, brain herniation and calcification.***
- ***The disadvantages of CT are radiation exposure and a limited diagnostic value in the evaluation of certain conditions such as early stroke, demyelinating disorders, neurometabolic disorders, infection and tumors.***
- ***MRI brain is preferred in patients with diffuse axonal injury, acute disseminated encephalomyelitis, posterior reversible encephalopathy syndrome and hypoxic ischemic encephalopathy.***
- ***Hypo attenuated lesions appear dark (hypodense) and lesions with high attenuation appear bright (hyperdense) on CT brain.***
- ***Children face an increased risk from CT radiation due to larger doses and increased lifetime radiation exposure. The risk of a leukemia three fold and triples the risk of brain cancer.***
- ***Though the benefits of CT outweigh the risks,it is imperative to reduce the dosage of radiation as much as possible.***
- ***Precautions to minimize radiation-related hazards are use of appropriate radio protective shields, applying ALARA principle (as low as reasonably achievable) to reduce radiation dose anduse of non-ionic contrast agents.***

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CLIPPINGS

Carbapenem-resistant bacteria in an intensive care unit during the coronavirus disease 2019 (COVID-19) pandemic: a multicenter before-and-after cross-sectional study

To assess the incidence of colonization and infection with carbapenemase-producing Enterobacteriaceae (CPE) and carbapenem-resistant Acinetobacter baumannii (CR-Ab) in the ICUs of the hospitals before and during the coronavirus disease 2019 (COVID-19) pandemic. Investigators conducted a multicenter, before-and-after, cross-sectional study to compare the rates of colonization and infection with CPE and/or CR-Ab in 2 study periods, period 1 (January-April 2019) and period 2 (January-April 2020). Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) of weekly colonization and infection rates for each period were compared for the 2 study periods using Poisson regression. Weekly trends in the incidence of colonization or infection for each study period were summarized using local weighted (Loess) regression. We detected no significant change in either IRR and weekly trend in CPE colonization and infection during the 2 study periods. A shift from KPC to other CPE mechanisms (OXA-48 and VIM) was observed during period 2. Compared to period 1, during period 2 the IRR of colonization and infection with CR-Ab increased 7.5- and 5.5-fold, respectively. Genome sequencing showed that all CR-Ab strains belonged to the CC92/IC2 clonal lineage. Clinical strains clustered closely into a single monophyletic group in 1 of the 3 centers, whereas they segregated in 2 different clusters in the other 2 centers, which strongly indicates horizontal transmission. Our findings indicate the need to conduct infection control activities targeted against the spread of antimicrobial resistance between and within hospitals during the COVID-19 pandemic, and if necessary remodulating them according to the new organizational structures imposed by the pandemic.

Pascale R, Bussini L, Gaibani P, Bovo F, Fornaro G, Lombardo D, et al . Carbapenem-resistant bacteria in an intensive care unit during the coronavirus disease 2019 (COVID-19) pandemic: a multicenter before-and-after cross-sectional study. Infect Control Hosp Epidemiol https://pubmed.ncbi.nlm.nih.gov/33858547.

IAP - IJPP CME 2021

PERIPHERAL SMEAR IN ANEMIA

Shanthi S

Abstract: *Peripheral smear is an important tool to diagnose hematological abnormalities. A good smear preparation and proper staining is vital for its correct interpretation. Many common causes of anemia like iron deficiency anemia, megaloblastic anemia and thalassemia can be diagnosed by a blood smear examination. This article discusses the basics of a good smear, methodical examination and interpretation of the smear in anemia.*

Keywords: *Anemia, Peripheral smear, Poikilocytosis, Iron deficiency, Thalassemia.*

The peripheral smear (blood film) and complete blood count are important investigations in any child with anemia. A good smear is important for proper interpretation. It is vital for the pediatricians to know the smear picture of common causes of anemia. Examination of a smear is an extension of the clinical examination in any hematological problem. Despite advances in automation and molecular diagnostics in hematology, the utility of peripheral smear examination cannot be overemphasized.

Technique of making a good smear (Fig.1)

Place a small drop of blood about 1 cm from one end of the slide. Either a finger prick sample or an EDTA sample (venous blood) can be used. If the latter is used, smears should be prepared as soon as possible. A delay can result in change in parasite morphology and staining characteristics. The slide should be clean, dry and should not be greasy. Place a spreader (another slide) in front of the drop at an angle of about 30° to the slide and move it back to make contact with the drop. The drop should spread out quickly along the line of contact. With a steady movement of the hand, spread the drop of blood along the slide. The spreader must not be lifted off until the last trace of blood has been spread out. Inconsistent pressure and use of an irregularly edged spreader may result in long tails. A greasy slide can result in lot of holes in the smear.

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Attributes of a good smear

A good smear is tongue shaped about 3 cm in length and has three components- the head, body and tail (Fig.2). The smear should stop at least 1 cm before the end of the slide. It has both thick and thin areas with a gradual transition. It should not contain any lines or holes.

The slide should be immediately labelled. Labelling can be done using a pencil on the thick portion of the slide. Write the name of the patient, the date of smear and any other identity number. Some slides have a frosted end for labelling.

Fixing the smear

It is important to fix the blood film to preserve the morphology of the cells. The film has to be dried before fixing it. Fixing is done by dipping in absolute methanol or ethanol for 30 seconds. It is especially important to fix the smear if it has to be dispatched by post to a distant laboratory. Methanol should not be used to fix a thick smear.

Types of smear

There are two types of smear- thick and thin.

Thick smear (Fig.3) is prepared by placing a drop of blood in the centre of the slide. Using the corner of another slide the blood is spread out in a circular motion to four times its original size. The smear is air dried for one hour in room temperature. The smear is of correct thickness if one can barely read a small print size when the slide is placed on a newspaper. The thick smear should neither be heat or methanol fixed. Thick films are generally not fixed before staining, as fixation would prevent osmotic lysis and dehemoglobinization.The thick smear consists of lysed red blood cells. This enables the parasites to be well seen. They are very useful when malarial parasites are scanty. Microfilariae can also be identified on a thick smear using a low-power objective. Five minutes of examination of a thick film is equivalent to about one hour examination of a thin film.

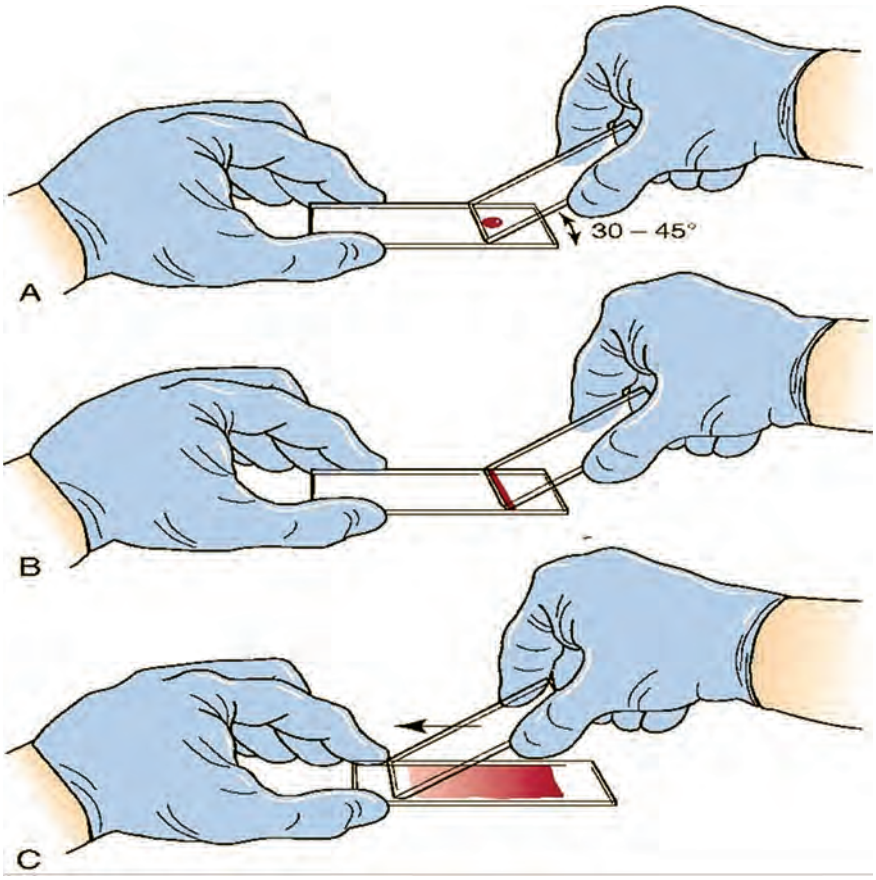

Fig.1. Technique of making a smear

(Source: Bamashmos SH, Moussa GH, Wadaane M, Najjar AE, Hamawy L, Elhalabi F Lebanon. Semi-Automated Blood Cell. Analysis Using Digital Image Processing. Conference paper: 17-19 October 2019 Fifth International Conference on Advances in Biomedical Engineering (ICABME), Tripoli, Lebanon).

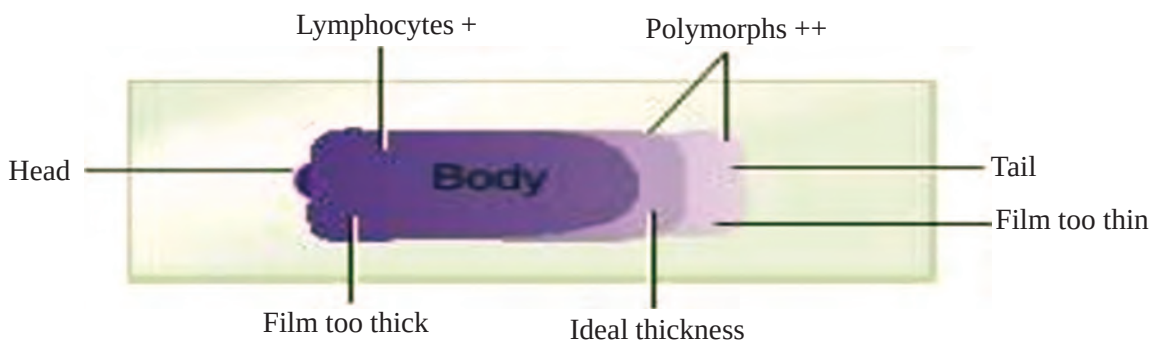

Fig.2. Parts of a smear

Thin film (Fig.4) is used to identify the species of malarial parasite and to assess the severity of *Plasmodium falciparum* infection, by counting the percentage of parasitized cells.

A wet film is sometimes used. A drop of blood is placed on a slide and a cover slip is applied. The edge of the coverslip is sealed using paraffin wax or nail varnish. Sodium metabisulphite can be added to hasten the sickling process. However sickling can occur even without addition of metabisulphite. It takes about 12 hours in trait. It is used to detect microfilariae, trypanosomes and spirochetes which can be actively moving. It is also used to identify sickling of red blood cells (RBCs) in sickle cell trait and

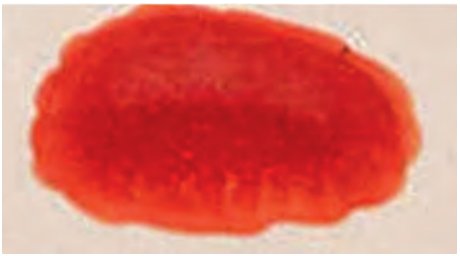

Fig.3. Thick smear

Fig.4. Thin smear

anemia. Rouleaux formation, autoagglutination and cryoglobulin can also be detected in a wet film.

Staining of the smear

There are many stains available. Romanowsky stains are commonly employed.

May-Grunwald stain, Jenner's stain, Giemsa's stain, Leishman's stain and Field's stain are examples of Romanowsky stain. Leishman's stain is the most commonly employed stain.

Method of staining: Air dry the film and flood the slide with the stain. After 2 minutes, add double the volume of water and stain the film for 5-7 min. Then wash it in a stream of water until it has acquired a pinkish tinge. Wipe the back of the slide and keep it upright to dry.

Automated staining machines are available that can handle many slides at a time. The instrument spreads, fixes and stains blood films.

Interpretation of the smear

For proper interpretation, the smear should be well spread, well stained and examined systematically. A methodical examination of all three blood cells namely red cells, white cells and platelets will give lot of information. It is important to know about the clinical history, clinical examination findings and complete blood count (CBC) including red cell indices for accurate interpretation of the smear.

The smear is first examined macroscopically to assess whether the spreading technique is good, staining is proper and if any abnormal particles are present (large platelet aggregates, cryoglobulin deposits or clumps of tumor cells).

Then the smear is inspected under low power (10X). This will give an idea of the quality of the preparation. Look for any red cell agglutination, excessive rouleaux formation or platelet aggregation. Assess the number, distribution and staining of the leucocytes. Leucocytosis and leucopenia are well appreciated in this field. Find an area where the red cells are evenly distributed and are not distorted. Identification of any blasts or nucleated red blood cells is possible by quickly scanning many fields.

Next, the smear is inspected under high power (40X). Major part of the assessment is done at this power. Abnormality in red cell size and shape, white cell morphology are well appreciated. Toxic granulation and vacuoles in the white cells are clearly seen. Manual differential count can be done under high power.

Finally the smear is inspected under oil immersion (100X). Finer details like Auer rods, basophilic stippling and examination of an unusual cell are checked. Unusual cell needs more detailed examination and minute details better visualised in oil immersion than under high power.

Red cells

They are examined in an area where there are no rouleaux formation and the red cells are touching each other and not overlapping. If the tail of the film is examined, a false impression of spherocytosis may be made.

Size: The size of the RBC corresponds to the size of the nucleus of the small lymphocyte. Difference in the size of the RBCS is known as anisocytosis. Microcytic RBCs (varies with age in children) are seen in iron deficiency anemia, thalassemia trait, lead poisoning, sideroblastic anemia and pyridoxine deficiency. Macrocytic (>95fL) RBCs are normally seen in the neonates. They are also

Box 1. Drugs causing macrocytosis

Reverse transcriptase inhibitors (zidovudine, lamivudine, stavudine)

Anticonvulsants (valproic acid, phenytoin),

Folate antagonists (methotrexate),

Chemotherapeutics (alkylating agents, pyrimidine and purine inhibitors)

Anti inflammatory (Sulfasalazine),

Pyrimethamine, trimethoprim, sulfamethoxazole, metformin

Nitrous oxide.

seen in megaloblastic anemia, liver disease, hypothyroidism, aplastic anemias, Down syndrome and myelodysplastic syndrome (MDS). Drugs causing macrocytosis are shown in Box 1.[1]

Most patients on treatment for HIV with reverse transcriptase inhibitors will have macrocytosis without anemia. Infact, macrocytosis is considered a surrogate marker of drug compliance by the patient.

Colour: Normochromia - The normal RBC is pink and has a central pallor which is about one third of the cell.

Hypochromia- The central pallor of the RBCs is increased to more than 50% of the diameter.[2] It is due to a lowered hemoglobin concentration and abnormal thinness of the red cells. It is typically seen in iron deficiency anemia (IDA), homozygous and heterozygous beta thalassemia and sideroblastic anemia. Leptocytes represent extreme forms of hypochromia.

Hyperchromia - The central pallor is lost. It is seen in spherocytosis, macrocytosis as seen in newborn and megaloblastic anemia due to increase in red cell thickness; mean corpuscular hemoglobin concentration (MCHC) is increased in spherocytes and normal in the other two conditions.

Anisochromasia - Here a dimorphic red cell population is present. Hypochromic and normochromic cells can be seen in recovering or early stages of iron deficiency anemia, when a patient with megaloblastic anemia also develops iron deficiency or after the transfusion of normal blood to a patient with hypochromic anemia and in sideroblastic anemia.

Polychromasia indicates the presence of increased reticulocytes. The nuclear remnants are stained blue. They are usually seen in hemolytic anemia.

Shape

Normal RBC is biconcave. If more than 10% of RBCs are of different shapes, it is known as poikilocytosis.[3]

The different shapes in the smear aid in diagnosis.

Spherocytes are smaller but thicker than normal. They lack the central pallor. If the tail of the film is examined, a false impression of spherocytosis may be made.

Target cells (codocytes) they have a central round stained area and a peripheral rim of hemoglobinised cytoplasm. These cells have disproportionately large surface compared with their volume. They occur due to impaired production of hemoglobin (Hb). They are seen in iron deficiency anemia, thalassemia, hemoglobin C disease, hemoglobin H disease, sickle cell anemia and hemoglobin E disease.

Elliptocytes (ovalocytes) are oval or cigar-shaped cells with blunt ends. They are seen in iron deficiency anemia, thalassemia, megaloblastic anemia and myelofibrosis.

Leptocytes (or wafer cells) are thin, flat cells with the hemoglobin at the periphery of the cell.

Teardrop erythrocytes (dacryocytes) are red cells with one end round and the other end more pointed.

Sickle cells (drepanocytes) are seen in freshly prepared blood smear of sickle cell anemia patients. They are often absent in neonates and are rare in adult patients with a high hemoglobin F percentage. Under anoxic conditions, massive sickling takes place. The sickled cells may be boat-shaped or appear as sickles.

In stomatocytes, the area of central pallor is elliptical instead of round, giving the cell the appearance of the opening of a mouth (stoma). They are seen in hereditary stomatocytosis, liver disease, alcoholism, use of certain drugs like hydroxyurea.

Irregularly contracted red cells may be seen in oxidant drug or chemical induced hemolytic anemias, some unstable hemoglobinopathies and hemoglobin E. These cells are smaller than normal, densely stained (lack central pallor) and their margins are slightly or moderately irregular.

A *blister cell,* also known as hemi-ghost cell is described in G6PD deficiency in which the hemoglobin appears to have contracted away from the cell membrane resembling a blister.

Red cell fragments and spiculated cells

They are the schistocytes, keratocytes, acanthocytes and echinocytes.

Schistocytes are seen in microangiopathic hemolytic anemia (MAHA), burns, megaloblastic anemia, dyserythropoietic anemias, thalassemia and pyropoikilocytosis. They are smaller than RBCs and of bizarre shape.

Keratocytes are sometimes described as helmet cells or bite cells. They occur due the removal of the Heinz bodies by the spleen. They have one or two pairs of spicules. They are seen in MAHA and G6PD deficiency.

Table I. Common abnormalities in shape of the RBC and underlying diagnosis.

Shape	Diagnosis
Sickle cell	Sickle cell disease
Spherocytes	Hereditary spherocytosis, auto immune hemolytic anemia, ABO incompatibility, burns, Clostridium perfringens infection, snakebite, hemolytic transfusion reactions
Pencil cells	Iron deficiency anemia
Macro ovalocytes	B12, folic acid deficiency
Elliptocytes	Hereditary elliptocytosis (>25%), pyropoikilocytosis, IDA, megaloblastic anemia
Stomatocytes	Hereditary stomatocytosis, liver disease
Schistocytes	Micro angiopathic hemolytic anemia (DIC, HUS, TTP)
Target cells	Thalassemia, IDA, hemoglobin C disease, liver disease,
Tear drop cells (dacrocytes)	MDS, myelofibrosis, myelophthisia (marrow infiltrations), extramedullary haemopoiesis, hereditary elliptocytosis, hereditary pyropoikilocytosis, severe iron deficiency, megaloblastic anemia, thalassemias
Acanthocytes	Liver disease, renal failure, abetalipoproteinaemia, pyruvate kinase deficiency

Acanthocytes (spur cells) have few spicules of inconstant length, thickness and shape, projecting from the surface of the RBC membrane at irregular intervals. They are present in abetalipoproteinemia, severe liver disease, McLeod syndrome, post splenectomy, hypothyroidism, and chorea acanthocytosis syndrome.[4]

Echinocytes (Burr cells): They are crenated RBCS. They have numerous short, regular projections from their surface. It is most commonly a storage artefact due to delay in preparing a smear or using an oily slide. If present in a smear made from fresh blood, it is always abnormal. Marked echinocytosis has been reported in premature infants after exchange transfusion or transfusion of normal red cells. Other causes include uremia, pyruvate kinase deficiency, liver disease, vitamin E deficiency.

The common abnormalities in shape of the RBC and their interpretation are shown in Table I.[5, 6]

Normoblasts are sometimes seen in the peripheral smear and indicates red cell hyperplasia in bone marrow.

Red cell inclusions comprise basophilic stippling, Howell-Jolley bodies, Pappenheimer bodies, Cabot's rings and Heinz bodies (seen only in supravital staining). Basophilic stippling or punctate basophilia indicates disturbed erythropoiesis. It can be seen in liver disease, megaloblastic anemia, thalassemia and lead poisoning. They appear as multiple purple blue dots (basophilic granules) inside the RBC. They represent fragmented ribosomal RNA or aggregates of ribosomes found precipitated throughout the cytoplasm.[7]

Howell-Jolly bodies are seen in asplenia, following splenectomy and in sickle cell anemia due to functional asplenia. They are nuclear remnants (DNA) and appear as a small, round, purple cytoplasmic inclusions.

Pappenheimer bodies are seen as black dots in the periphery of the RBC. They contain hemosiderin (iron) and are seen in sideroblastic anemia. They are smaller than Howell-Jolly bodies. They stain blue with Perl's stain.

Cabot rings: These are mitotic spindle remnants seen as ring-shaped or as figure-eight inclusions. They can be seen in megaloblastic anemia, myelodysplasia and other forms of dyserythropoiesis.

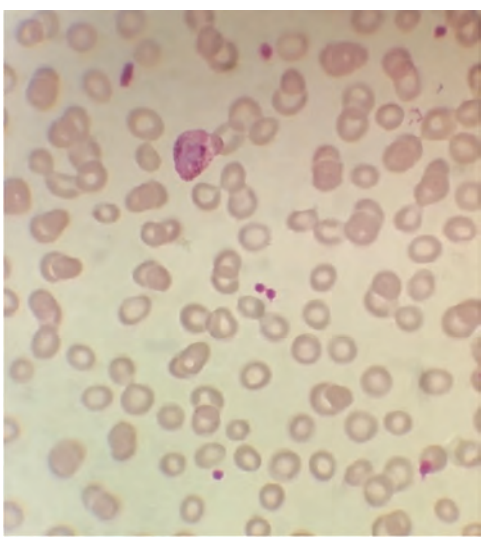

Fig.5. Plasmodium vivax-schizont

Hemoglobin C crystals: They are dense rectangular structures composed of precipitated hemoglobin C present in hemoglobin C disease. They can be seen extracellularly or inside the RBC.

Heinz bodies occur secondary to oxidant damage and represent degraded haemoglobin. They are seen following chemical poisoning, drug toxicity, glucose-6-phosphate dehydrogenase (G6PD) deficiency or in the presence of an unstable haemoglobin. They are visible only with supravital staining.

Hemoglobin H inclusions are seen in alpha-thalassemias giving rise to the characteristic 'golf ball' appearance of the erythrocytes.

Malarial parasites are first identified in the thick smear and the species identification is done in the thin smear (Fig.5). The trophozoites, schizonts and gametocytes of different species differ. Identification of a malarial parasite needs careful scrutiny of at least hundred fields. A positive result is rewarding, may avoid unnecessary investigations in a sick child and can help in specific management.

Rouleaux formulation and autoagglutination

Rouleaux are aggregations of RBCs seen when the erythrocyte sedimentation rate is increased in infections, cancers, and inflammatory conditions.

Increased rouleaux formation is seen in multiple myeloma and macroglobulinemia. Autoagglutination is seen in cold hemagglutinin disease.

White blood cells

The number of white cells is assessed. Generally there are about 2-5 WBCs/high power field. Leucopenia is better appreciated under low power. Differential count may have to be done manually when there is a flag in the CBC, as the automated counter will count nucleated RBCs as WBCs. Stabs or band forms, cytoplasmic granules or vacuoles are present in severe sepsis. Presence of blasts in peripheral smear indicates leukemia. Hyper segmented polymorphs (six or more lobes or the presence of more than 3% of neutrophils with at least five lobes[5]) are seen in megaloblastic anemia. Presence of giant granules in the cytoplasm of polymorphs or other WBCs may point to a diagnosis of Chediak Higashi syndrome in a child with anemia and partial albinism.

Platelets

Platelets are tiny pink granules seen in single and clumps. Presence of good clumps indicate adequate platelet function. Platelet numbers, size and presence of clumps should be checked. A single platelet in an oil immersion field roughly corresponds to 10,000cells/mm^3. Thrombocytopenia can be present in megaloblastic anemia. Iron deficiency anemia may be associated with thrombocytosis.

In most children with anemia, the white cells and platelets are normal. In bone marrow aplasia all cell lines are affected. In marrow infiltration as in leukemias, the white cell count may be normal, decreased or increased; there is anemia and thrombocytopenia. Bicytopenia or aplasia in a child with anemia often warrants a bone marrow examination. A careful examination of the smear, history, clinical examination and a CBC picture often clinches the diagnosis in most cases of anemia.

The smear finding in common causes of anemia is described below

1. Iron deficiency anemia (Fig.6). - smear shows severe anisopoikilocytosis, microcytic hypochromic RBCs; elliptocytes, pencil cells, target cells, basophilic stippling may also be seen. The number of RBCs are reduced in severe iron deficiency anemia.
2. Thalassemia (Fig.7) - smear shows severe anisopoikilocytosis, microcytic hypochromic RBCs, polychromasia, target cells and many normoblasts.
3. Megaloblastic anemia - smear shows anisopoikilocytosis, macro ovalocytes and hypersegmented polymorphs. In advanced cases, leucopenia and thrombocytopenia can occur
4. Hereditary spherocytosis (Fig.8) - anisopoikilocytosis, polychromasia, occasional normoblasts and many spherocytes

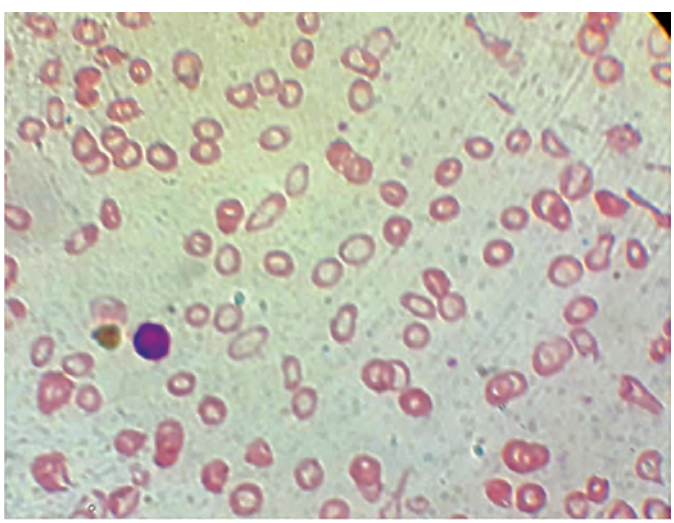

Fig.6. Iron deficiency anemia

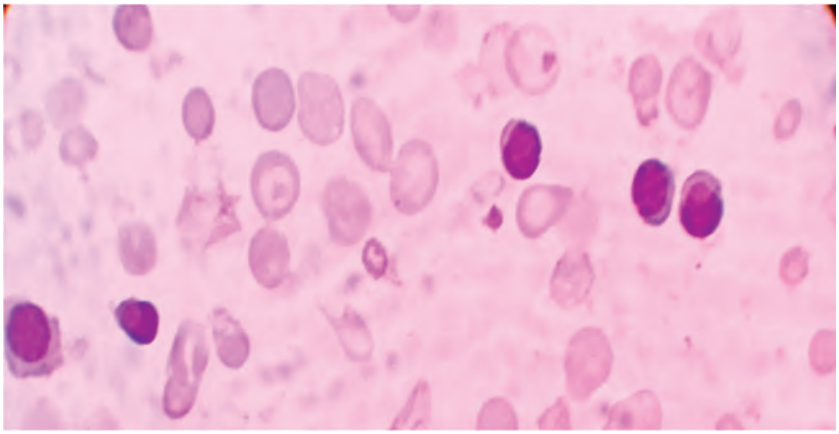

Fig.7. Thalassemia

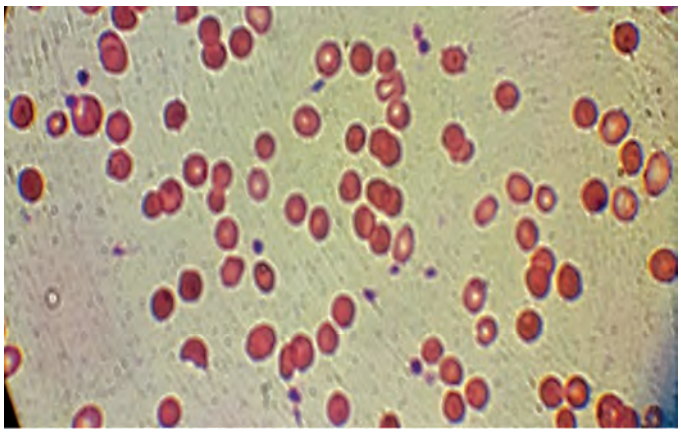

Fig.8. Hereditary spherocytosis

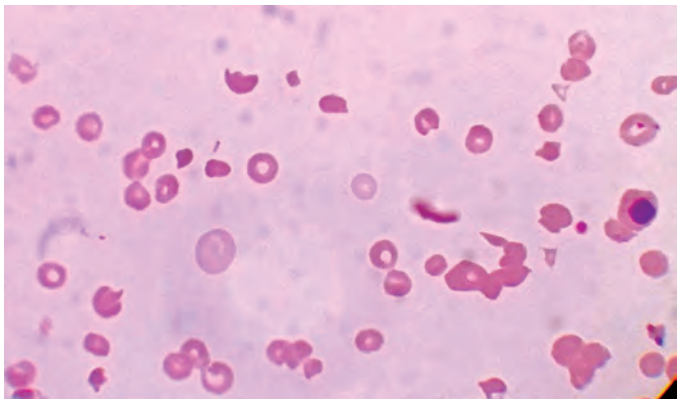

Fig.10. Hemolytic uremic syndrome showing schistocytes

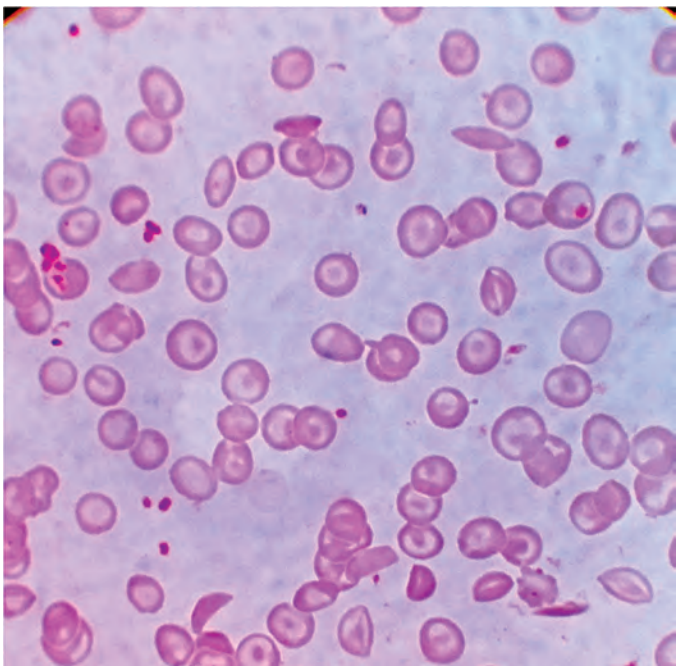

Fig.9. Sickle cell anemia

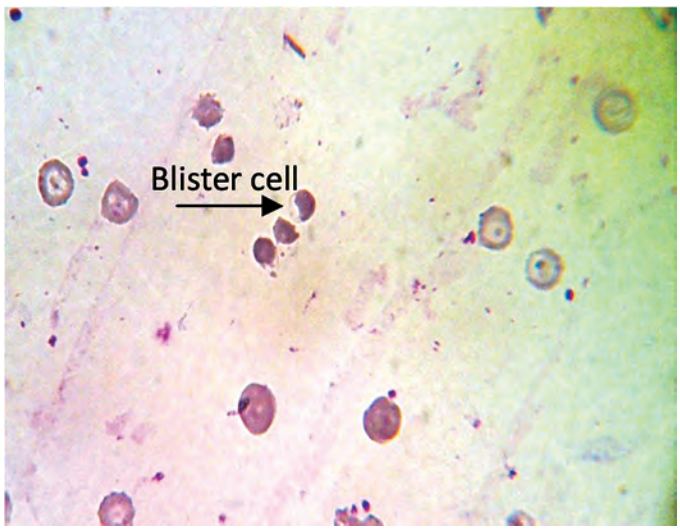

Fig.11. G-6PD deficiency (Courtesy: Dr.Indumathy)

5. Sickle cell anemia (Fig.9) - anisopoikilocytosis, normocytic, normochromic RBCs, polychromasia, occasional normoblasts, target cells and sickle cells

6. Microangiopathic hemolytic anemia (HUS) (Fig.10) - smear shows anisopoikilocytosis, polychromasia, normoblasts and many fragmented RBCs (schistocytes

- helmet cells, small, irregular triangular, or crescent-shaped cells, pointed projections and lack of central pallor and thrombocytopenia.

7. G6PD deficiency (Fig.11) - smear may show anisopoikilocytosis, polychromasia, bite cells, blister cells and schistocytes. Normoblasts are usually seen. Heinz bodies may be seen in supravital staining. Peripheral smear is the gold standard in diagnosing G6PD deficiency in patients with first episode of acute hemolytic crisis.

Points to Remember

- ***A good smear technique and proper staining is essential for correct interpretation.***
- ***Methodical examination of all three cell lines is crucial.***
- ***Poiklocytosis refers to abnormal shape in RBC and anisocytosis to difference in size.***
- ***Many inherited anemias like thalassemia, sickle cell anemia and hereditary spherocytosis can be diagnosed by careful examination of a peripheral smear.***
- ***A smear should always be interpreted in collaboration with history, clinical findings and CBC report.***

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CLIPPINGS

Modified Brixia chest X-ray severity scoring system and correlation with intubation, non-invasive ventilation and death in a hospitalised COVID-19 cohort

There are few existing severity scoring systems in the literature, and no formally widely accepted chest X-ray template for reporting COVID-19 infection. Study aimed to modify the chest X-ray COVID-19 severity scoring system from the Brixia scoring system with placement of more emphasis on consolidation and to assess if the scoring tool could help predict intubation. A severity chest X-ray scoring system was modified from the Brixia scoring system. PCR positive COVID-19 positive patient's chest X-rays admitted to our hospital over 3months were reviewed and correlated with; non-invasive ventilation, intubation and death. An analysis was performed using a receiver operating curve to predict intubation from all admission chest X-rays. The median score of all 325 admission chest X-rays was 3 (Interquartile range (IQR) 0-6.5). The median score of admission chest X-rays of those who did not require ICU admission and survived was 1.5 (IQR 0-5); and 9 (IQR 4.75-12) was median admission score of those requiring intubation. The median scores of the pre-intubation ICU chest X-rays was 11.5 (IQR 9-14.125), this increased from a median admission chest X-ray score for this group of 9 (P-value<0.01). A cut-off score of 6 had a sensitivity of 77% and specificity of 73% in predicting the need for intubation. The higher chest X-ray severity scores are associated with intubation, need for non-invasive ventilation and death. This tool may also be helpful in predicting intubation

Hanley M, Brosnan C, O'Neill D, Ni Mhuircheartaigh N, Logan M, Morrin MM, et al.Modified Brixia chest X-ray severity scoring system and correlation with intubation, non-invasive ventilation and death in a hospitalised COVID-19 cohort .Journal of Medical Imaging and Radiation Oncology (https://pubmed.ncbi.nlm.nih.gov/34845851).

GENERAL ARTICLE

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS - AN UPDATE

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***Manish R. Garg
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Abstract: *Attention deficit hyperactivity disorder is one of the most common neurobehavioral disorders of childhood. This is an update on the latest 2019 guidelines American Academy of Pediatrics and will focus on the changes from the previous 2011 guidelines.*

Keywords: *AAP guidelines 2019, ADHD, Diagnosis, Treatment.*

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders of childhood which can profoundly affect social interactions, wellbeing and academic achievement of the child.[1] The 2011 guidelines on ADHD by American Academy of Pediatrics (AAP) which were based on Diagnostic and Statistical Manual of Mental Disorders (DSM–4) criteria have been revised in 2019 based on DSM-5 criteria.[2,3] This review will focus on 2019 guidelines and the changes from the previous guidelines (Table I.) followed by an assessment of the Indian scenario.

Salient features of the 2019 guidelines

The key differences in recent guidelines over 2011 guidelines include inclusion of DSM-5 criteria, special guidance for preschool aged children (4-6 years) and adolescents, highlights on neuropsychological testing and pharmacogenomics and elaboration of non-pharmacological therapies.[3]

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Evaluation and diagnosis of ADHD

The guidelines state that any child or adolescent (4-18 years) presenting with academic or behavioral problems, symptoms of inattention and hyperactivity or impulsivity should be evaluated for ADHD due to its high prevalence. Diagnosis should be based on DSM-5 criteria with documented impairment in more than one major setting (i.e. social, academic, or occupational) with alternative causes being ruled out. A special focus is laid on screening of co-morbid conditions and mimics of ADHD like substance abuse especially in adolescents which can alter the treatment. There is insufficient evidence regarding the role of neuropsychological testing for diagnosing ADHD other than ruling out comorbid conditions like learning disorders.

Special considerations for adolescents / pre-schoolers / problem behaviours

In adolescents, the manifestations of ADHD should have been present before 12 years of age, instead of 7 years as stated in previous guidelines. For preschoolers (4-6 years) where symptoms are not certain, DSM-5 should be applied after parent training for behavioral modifications (PTBM) for effectively dealing with problem behaviors. Further, there is insufficient evidence to recommend diagnosis or treatment for children younger than 4 years but they should be referred for PTBM in presence of behavioral concerns. Children with behavioral problems not meeting the DSM-5 criteria should be closely reviewed, mimics of ADHD should be ruled out and behavioral interventions, such as PTBM, can be initiated.

Treatment (Fig.1)

For preschool children (4-6 years) with ADHD, behavioral therapy is the first line of treatment. Methylphenidate is to be considered as second line only for those not responding to behavioral therapy with moderate to severe impairment in functioning.

In children (6-12 years) with ADHD, FDA approved medications along with parent training in behavior management (PTBM) or behavioral classroom interventions should be prescribed. Adolescents (12-18 years) should be prescribed FDA approved

Table I. Comparison of 2011 and 2019 guidelines on diagnosis of ADHD

	2011 Guidelines	2019 guidelines
Diagnosis	Clinician should determine that DSM-4 criteria are met	Clinician should determine that DSM-5 criteria are met
Diagnosis in special circumstances		
Preschool children	The diagnostic criteria of ADHD can be applied to preschool children, but the subtypes in DSM-4 may not be valid in them	The diagnostic criteria of ADHD can be applied to preschool children
	Only Conners comprehensive behavior rating scale or ADHD Rating Scale IV are the DSM-4 scales validated in preschool children	If ADHD rating scale - V or ADHD rating scale - IV preschool version is not available, any DSM based scale can be used
	Physicians may recommend complete parent training program before confirming the diagnosis of ADHD. Qualified preschool programs - Head start or other public pre-kindergarten programs.	Parent training in behavioural management (PTBM) is the recommended primary intervention for preschool children with ADHD or ADHD like symptoms to be implemented before applying DSM-5 criteria for diagnosis.
Adolescents	It is unusual for adolescents with behavioral /attention problems not to have been previously given a diagnosis of ADHD. Therefore, it is important to establish the younger manifestations of the condition that were missed.	They must have some reported or documented manifestations of inattention or hyperactivity/ impulsivity before age 12, unless they previously received a diagnosis, to meet DSM-5 criteria for ADHD.
	Clinicians should strongly consider substance use, depression and/or anxiety as alternative or co-occurring diagnosis	Clinicians should strongly consider whether a mimicking or comorbid condition, such as substance use, depression and/or anxiety is present. Certain substances, such as marijuana, can have effects that mimic ADHD Trauma experiences, post-traumaticstress disorder and toxic stress are additional co-morbidities and riskfactors of concern
Special circumstances: Inattention or hyperactivity/ Impulsivity (Problem Level – i.e., in attention and / hyperactivity not meeting the DSM criteria for ADHD)	Diagnostic and Statistical Manual for Primary Care (DSM-PC) provides a guide to common behaviors in children	DSM-PC cannot be used as a definitive source for diagnostic codes related to ADHD since it has not been revised to be compatible with DSM-5

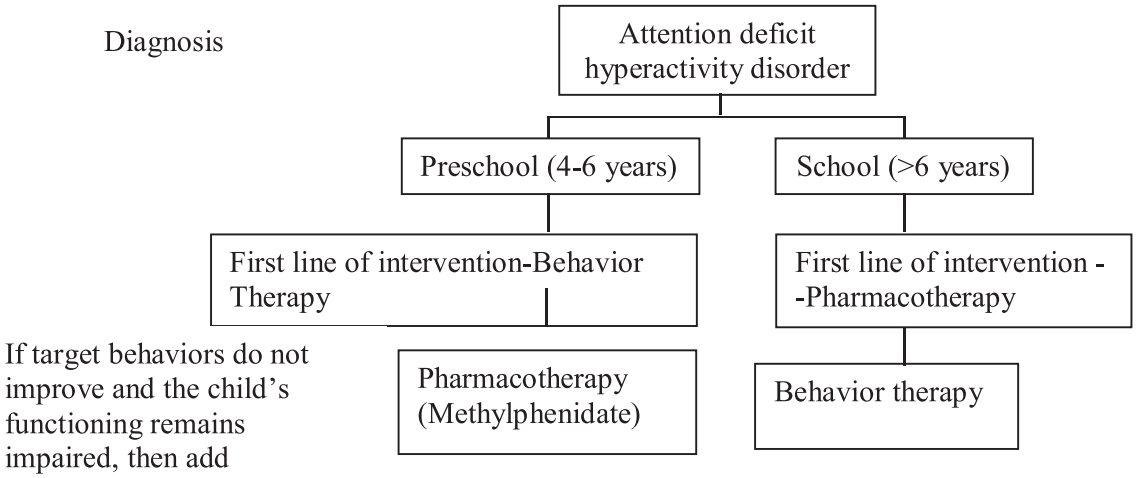

Fig.1. Treatment guidelines for ADHD

Table II. Comparison of treatment guidelines of 2011 and 2019 on treatment

Age	2011	2019
Preschool children	Evidence based parent / teacher administered behavior therapy is the first line of treatment	First line of therapy is evidence based <6 years behavioral therapy (PTBM) and/or behavioral classroom interventions
6-12 years	Should prescribe US Food and drug administration (FDA) approved medications for ADHD and / or evidence-based parent / teacher administered behavior therapy particularly both	Should prescribe US Food and drug administration (FDA) approved medications for ADHD, along with PTBM and/or behavioral classroom intervention (preferably both PTBM and behavioral classroom interventions). Educational interventions and individualized instructional supports such as school environment, class placement, instructional placement and behavioral supports are necessary part of any treatment plan. This also includes an individualized education program (IEP) or a rehabilitation plan.
Adolescents	Behavior therapy - Grade C recommendation	The PCC is encouraged to prescribe evidence-based training interventions and/orbehavioral interventions as treatmentof ADHD, if available. (Grade A recommendation)

medications and encouraged for behavioral or training interventions. Combination therapy with medications and behavior/psychological therapy is superior to behavior/ psychological therapy alone and necessary for restoration of function. Medication is not appropriate for children whose symptoms do not meet DSM-5 criteria for ADHD.

It is recommended to treat ADHD as a chronic illness and provide continuity of care, and where possible, provide a medical home. The concept of 'medical home' (as advocated by AAP) refers to a comprehensive, patient centered and coordinated care which integrates both physical and mental health and provides long term assistance and support. A strong family-school partnership is encouraged as a part of ADHD management process.

Non-pharmacological treatment

Behavioral treatments, especially PTBM (Table II), have a strong level of evidence in preschoolers with ADHD and even in those with problem behaviors not meeting ADHD criteria regardless of etiology.

In older children and adolescents, the level of evidence for behavioural therapy is not so strong and various approaches, including involvement of adolescent with parents during PTBM sessions, behavioural classroom interventions, educational interventions and individualized instructional supports like individualized education program (IEP), motivational interviewing and training approach focusing on skills as regards to school executive functioning. Nonetheless, ongoing adherence to psychosocial treatment is the key to its effectiveness.

Other treatments like mindfulness, cognitive training, diet modification, EEG biofeedback, external trigeminal nerve stimulation (eTNS) and supportive counseling have too little evidence for their recommendation.

Medications

The FDA approved medications for children above 6 years include stimulants like methylphenidate, dextroamphetamine, amphetamine and non-stimulants like atomoxetine, guanfacine and clonidine.

For preschoolers, methylphenidate has moderate evidence for efficacy and safety but is used off-label; other stimulants and non-stimulants are not recommended due to insufficient evidence. Above 6 years, evidence for stimulants is the strongest (effect size 1.0) followed by non-stimulants (effect size 0.7) and is not influenced by ADHD subtype. Only extended release guanfacine and clonidine have evidence supporting their use as adjunctive therapy with stimulants.

Calculating dose on the basis of milligrams per kilogram is discouraged due to variable effects unrelated to height and weight and hence titration from low dose is advised. In adolescents, emphasis has been laid on evaluation for substance abuse before initiating medication.

Due to the large variability in patients' response to ADHD medication, there is great interest in pharmacogenetic tools for assessment of polymorphisms in drug metabolizing enzymes which could predict potential drug interactions and adverse idiosyncratic drug reactions. However, there is lack of sufficient evidence to recommend their routine use at present.

Future implications

Key areas identified for future research include development of tools for assessment of functional impairment and comorbid condition by primary care physicians, developing more objective performance indicators and web based electronic systems for data collection and monitoring treatment along with studies focussing on effectiveness of cognitive behavioral therapy, cognitive training and school based interventions.

The Indian perspective

In India, the prevalence rates of ADHD vary in different studies from 4.7-29.2% with male to female ratio varying from 1.8:1 to 7.4:1.[4] A retrospective study of 1301 children presenting with developmental concerns from a centre in Mumbai identified 422 (32.4%) children with ADHD.[5]

In India, low level of awareness among parents, doctors and teachers leads to ADHD remaining undiagnosed with a mean delay in diagnosis of 3.96 years.[6,7] This is further compounded by intrusion of extended families influencing parental perceptions, varying tolerance to developmental deviances among different cultures and social stigma for seeking psychiatric help. A study analysing the relevance of the ADHD diagnostic construct in the Indian setting highlighted that the majority of referrals were related to academic difficulties, and many parents, even after recognizing difficulties, did not primarily consult with doctors and attributed their child's problems to learning and memory difficulties. Also, rejection of diagnosis when first conveyed to them was common.[8] Teacher's assessment of the child's behaviour may not be accurate due to the high student-teacher ratios in Indian schools.[6]

In clinical practice, diagnostic tools (i.e. Child behavior check-list, Conners abbreviated rating scale and Vanderbilt ADHD diagnostic parent rating scale) have not been validated in the Indian population. The only freely available indigenous tool is the revised INCLEN Diagnostic Tool for ADHD (INDT- ADHD) which has been recently developed.[9]

Challenges faced during treatment include reluctance to use psychotropic medication by parents and non-adherence due to side effects, perceived lack of effectiveness due to insufficient dosing and titration, fear of the child getting addicted, problems in accessing medication and cost.[10] Challenge to effectiveness of behavioural therapy include inconsistency in implementing behavioral interventions by all adults at home in a joint family and preference of educational and religious treatments over behavioral interventions by parents.[8,10]

As yet, the Persons with Disability Act, 1995 and the National trust for the welfare of persons with autism, cerebral palsy, mental retardation and Multiple Disabilities Act, 1999, do not recognize ADHD as a neurodevelopmental disorder and there are no provisions for certifying children with ADHD. However, the Rashtriya

Bal Swasthya Karyakram (RBSK) includes ADHD among its list of conditions.[11]

An overview of research from India had revealed that although ADHD research is on the rise for the last two decades, most of the studies were cross-sectional in design, with small sample size or longitudinal with short follow up periods or lack of adherence to treatment and based in hospital or school settings.[4] There were many studies regarding efficacy of ADHD medication in Indian population and their results were in line with international data showing superiority of methylphenidate.[4] However, most of the studies on non-pharmacological interventions, have studied them as an add on to the pharmacological management. Also, there is a paucity of RCTs (randomized controlled trials) as well as limited studies in community setting and on adults with ADHD.[4]

To conclude, the increasing impact of ADHD on children and their family call for measures to increase awareness and strengthen research to evaluate disease trends and effects of behavioral intervention and medications. Further, "parent preferences" for educational interventions over psychiatric interventions for ADHD calls for restructuring of early intervention programs within a school context. Increasing collaboration between schools and developmental pediatricians or mental health professionals, is needed with more research into preventive strategies that could be implemented in school settings for at risk children.

Points to Remember

- ***Diagnosis of ADHD as per AAP guidelines-2019 should be based on DSM-5 criteria with documented impairment in more than one major setting and alternative causes ruled out.***
- ***In adolescents, the manifestations of ADHD should have been present before 12 years of age instead of 7 years as stated in previous guidelines.***
- ***A special focus is laid on screening for co morbid conditions and mimics of ADHD such as substance abuse especially in adolescents which can alter the treatment.***
- ***For preschool children (4-6 years) with ADHD, behavioral therapy is the first line of treatment. Methylphenidate is to be considered as second line.***
- ***In children (6-12 years) with ADHD, FDA approved medications along with behavioral therapy or behavioral classroom interventions should be prescribed.***
- ***There is insufficient evidence to recommend diagnosis or treatment for children younger than 4 years, but they should be referred for behavioral modification in presence of behavioral concerns.***

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DRUG PROFILE

USE OF INOTROPES IN PICU

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Abstract: *Inotropes increase myocardial contractility and have variable effects on peripheral vascular resistance. The first-line inotropic agents used in pediatrics are dopamine and epinephrine. Further, depending on cardiac output and systemic vascular resistance, other vasoactive agents indicated in the treatment of shock in children include vasoconstrictors (e.g. norepinephrine, phenylephrine) or vasodilators (e.g. dobutamine, milrinone). The effective inotrope indicated for the given etiology of shock depends on the end-diastolic volume and cardiac contractility. This article attempts to throw light on appropriate use of these agents.*

Keywords: *Inotrope, Epinephrine, Dopamine, Norepinephrine , Isoprenaline, Vaspressor, Bipyridines*

Disorders of cardiorespiratory system is quite common in pediatric critical care. Such children frequently require pharmacological support to maintain end-organ perfusion. This could be achieved either by increasing myocardial contraction (positive inotropy), increase in rate of contraction dromotropy, improving relaxation of myocardium during diastole in diastolic heart failure (lusitropy), increasing vascular tone (vasoconstriction) in vasodilatory shock or decreasing the same (afterload reduction) in hypotensive shock associated with vasoconstriction. Many at times a combination of effects may be needed depending on physiological state of patient. The pharmacological agents used to achieve this have both desirable and less desirable effects like increase in heart rate (chronotropy) or excessive vasoconstriction leading to skin necrosis and elevated afterload for heart increasing myocardial oxygen demand and fatigue.[1,2] Hence a detail knowledge of these agents is required in order to use them in a safe and effective manner.

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Classes of drugs[3]

Cardiovascular supportive pharmacological agents can be studied in following classes:

- Catecholamines: endogenous compounds (adrenaline, nor-adrenaline, dopamine) and synthetic products (isoproterenol and dobutamine)
- Bipyridines: milrinone and inamrinone
- Vasopressors: vasopressin and terlipressin
- Glycosides: digitalis
- Ca sensitizer: levosimendan, calcium.
- Afterload reducing agents: glyceryl trinitrate (GTN), hydralazine, sodium nitropruside.
- Sympathomimetic: phenylephrine, ephedrine.

Mechanism of action

The final common mediator for both processes is the concentration of calcium in the cytosol (Fig.1 and Fig.2). The pathway by which pharmacologic agents affect this parameter is a function of their specific cell surface receptors.[4]

Catecholamines modify cellular physiology by interacting with a specific adrenergic receptor. Adrenergic receptors mediate their effects through G proteins and as such are classified as G protein coupled receptors. Types of G proteins: Gs, Gi, or Gq. Gs proteins produce an increase in adenylate cyclase activity, while Gi proteins promote a decrease in adenylate cyclase activity. Gq protein receptors stimulate phospholipase C to generate diacylglycerol and inositol 1,4,5-triphosphate (Fig.1 and 2, Table I,II,III).[5,6,7]

Vasopressin receptors (V1,V2,V3), vasopressin is released in response to increase in plasma osmolality, decrease in blood pressure (BP) or blood volume.[8] Vasopressin can produce vasoconstriction by acting on V1 receptors on vascular beds. It also acts on V1 receptors in CNS causing reflex bradycardia. V1 receptors are G-protein coupled receptors leading to rise in intracellular

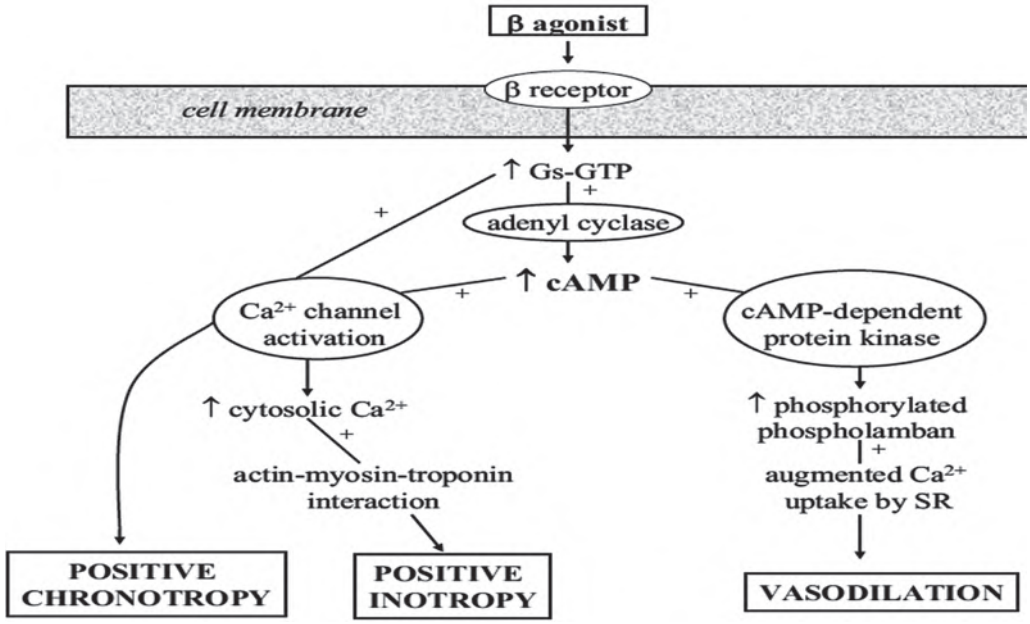

Fig.1. Mechanism of action of beta agonist

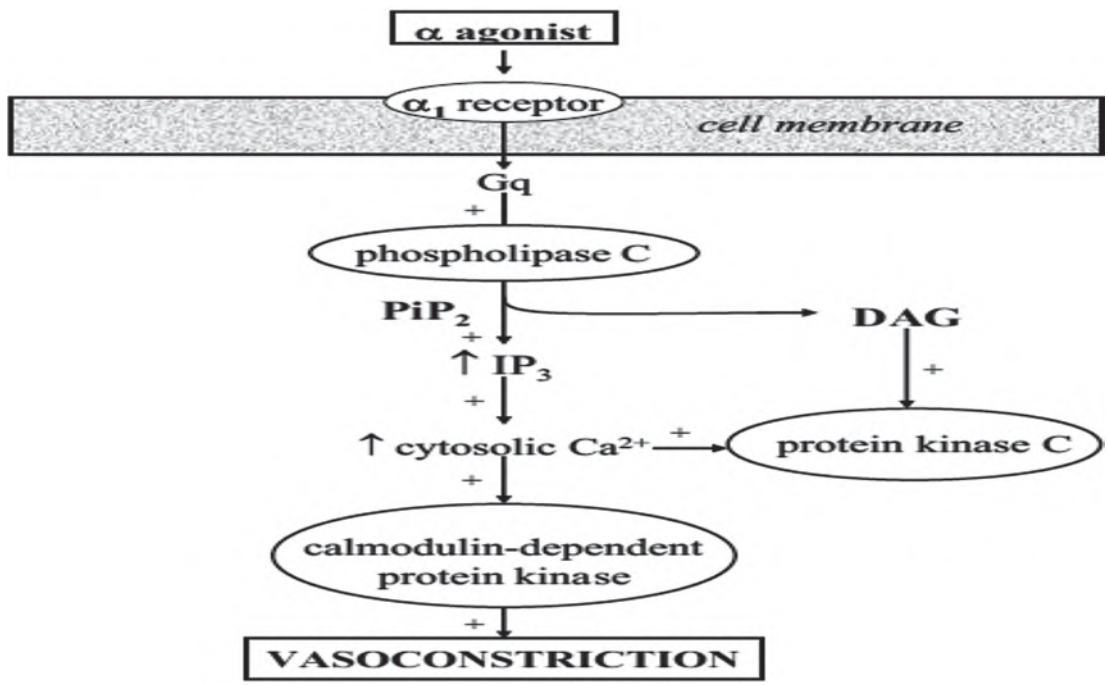

Fig.2. Mechanism of action of alpha agonist

Ca and weak positive inotropy. It also increases pressor effect of catecholamine (Table III).[9]

Phosphodiesterase regulation of cAMP: They catalyse conversion of cAMP to AMP, decreasing level of cAMP, protein kinase A (PKA) and hence intracellular Ca. Phosphodiesterase III (PDE3) is present on many cells including cardiac myocytes and vascular smooth muscle cells. It is specific for cAMP. Bipyridines competitively inhibits PDE3 preserving higher cAMP level which results in positive inotropic effect on myocardium and vasodilatory effect on systemic and pulmonary vasculature (Fig.3, Table III).[10]

Inotropic sympathomimetics

Dopamine hydrochloride has a variable, unpredictable, and dose dependent impact on vascular tone.[4] Low dose

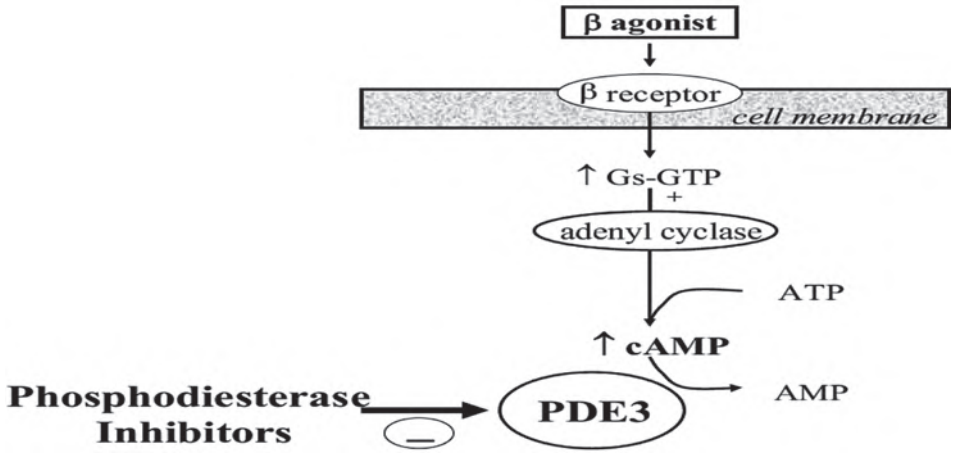

Fig.3. Mechanism of action of phosphodiesterase inhibitors (bipyridines)

Table I. Adrenergic receptors: Physiologic responses, agonist potency, and representative antagonists. (E-Epinephrine, NE-Norepinephrine, D-Dopamine, I-Isoproterenol)[11]

Receptor	G Protein	Physiologic response	Agonist	Antagonist
α1	Gq	Increase InsP3, 1,2-DG and intracellular Ca+2: muscle contraction, vasoconstriction	E > NE > D	Prazosin
α2	Gi	Decrease cAMP; inhibit NE release, vasodilation, negative chronotropy	E>NE	Yohimbin
β1	Gs	Increase cAMP; inotropy, chronotropy	I > E ≥ D ≥ NE	Propranolol, metoprolol
β2	Gs	Increase cAMP; smooth muscle relaxation; vasodilation; bronchodilation; hypokalemia	I ≥ E > D > NE	Propranolol
D1	Gs	Increase cAMP; smooth muscle relaxation	D	Haloperidol, metoclo-pramide
D2	Gi	Decrease cAMP; inhibit prolactin and β-endorphin	D	Domperidone

cAMP, Cyclic adenosine monophosphate; D, dopamine; 1,2-DG, 1,2 diacylglycerol; E, epinephrine; I, isoproterenol; InsP3, Inositol 1,4,5-triphosphate; NE, norepinephrine

Table II. Relative effects of various catecholamine drugs

	Inotrope	Chronotrope	Vasoconstriction	Vasodilation
Epinephrine	+++	++	++	+
Norepinephrine	+	**0**	+++	**0**
Isoprenaline	+	+++	**0**	+
Dopamine	++	++	++	**0**
Dobutamine	+++	++	**0**	++

infusion normally causes vasodilatation, but there is little evidence that this is clinically beneficial; moderate doses increase myocardial contractility and cardiac output in older children. High doses cause vasoconstriction and increase vascular resistance (Table III) and should therefore be used with caution following cardiac surgery. If hypotension in septic shock persists after volume replacement with crystalloids or colloids, dopamine hydrochloride may be started (Table V).

Table III. Basic drug details[12]

Drug	Clinical pharmacology / Pharmacokinetics	Clinical role	Adverse effects	Practical consideration
Dopamine (D1, D2, β1, β2 agonist)[13,14]	1-10 mcg/kg/min-rise in stroke volume without major effect in HR and BP (chronotropic and inotropic effect). >10 mcg/kg/min - vasoconstriction T1/2 with normal kidney function - 2 minutes Critically ill children - 26 min Neonates - 5 to 11 minutes	Effective inotropic and vasopressor Vasodilator at lower doses (dopaminergic and β receptors)	Tachyarrhythmia Supress production of of thyroid, prolactin and growth hormone Worsening of limb ischemia and gangrene if given in peripheral vessel	Used to treat mild to moderate cardiogenic or distributive shock with moderate hypotension however not the first line agent. Epinephrine is preferred more
Epinephrine (α1, α2, β1, β2 agonist)[15,16,17,18]	Acts more on the β-receptors than on the α-receptors 0.05-0.5 mcg/kg/min - increase BP by increasing HR and contractility, also improves stroke volume by β2 mediated decrease in SVR 0.1-1 mcg/kg/min - increases vascular resistance but balanced by improved cardiac output and activation of vascular β2 receptor 1-2 mcg/kg/min - significant α1 mediated vasoconstriction, impared organ blood flow and impaired myocardial function Metabolic effects - hyperglycemia, hyperlactatemia, hypokalemia. T1/2- 1 minute	Most useful when hypotension exist with low cardiac index Agent of choice for shock after ROSC following cardiac arrest	Enhanced automaticity and potential arrhythmia Increased myocardial oxygen consumption. Increase in PVR at high doses hence RV afterload	Most common indication in PICU-cardiogenic shock, septic shock with decreased stroke volume and shock following hypoxemia-ischemia Less chances of vasospasm and local tissue injury due to β2 activation (Table II) More potent and safer that Dopamine or Dobutamine
Norepinephrine (α1, α2, β1 agonist)[19,20]	Elevates SVR as α agonism is not opposed by β2 stimulation. Does have inotropic effect mediated by β1 action butreflex vagal activity reduces sinus node discharge blunting β1chronotropic effect. T1/2- 2 minutes	Improves perfusion in children with hypotension and normal or elevated cardiac index Most valuable in context of tachycardia	Increase in afterload may increase O2 consumption but reflex decrease in HR decreases reduce it and also improves diastolic coronary perfusion Injudicious use just to increase BP in low cardiac index or stroke volume condition may cause multiple organ system failure	Agent of choice for hypotension with abnormally low SVR and a normal or high cardiac output after adequate fluid resuscitation: Septic shock and other distributive shock

Drug	Clinical pharmacology / Pharmacokinetics	Clinical role	Adverse effects	Practical consideration
Dobutamine (Predominant β1 agonist)[23,24,25]	Significant inotropic and trivial chronotropic and vasodilation activity T1/2- 2 minutes	May be used in myocardial dysfunction associated with hyperdynamic shock: ARDS or septic shock	Tachycardia and increases myocardial O2 demand especially when myocardial contractility is normal Hypotension Ectopics	Reserved to treat poor myocardial contractility, however less commonly used due to availability of safer drugs like Milrinone Can be given peripherally
Isoproterenol (b1 & b2 agonist)[32]	Enhance inotropy and chronotropy Fall in SVR Bronchodilation	Limited utility due to adverse effects and availability of safer drugs	Significant tachycardia, increase in myocardial O2 demand and decrease supply by reducing diastolic time	May play a role in treatment of symptomatic bradycardia
Vasopressin (ADH agonist in arterioles)[21,22]	Dramatic increase with rise in plasma osmolality above 280 mOsm/kg. Higher threshold for release in response to hypovolemia or hypotension Acts on V1a rec, Gq mediated-rise in intracellular Ca. T1/2- 10 to 20 min, prolonged in renal failure and hepatic insufficiency	Used for vasodilatory shock, to improve blood pressure, increase SVR, lessen the need for catecholamine	Elevation in liver enzymes, total bilirubin, decrease in platelet count Ischemia of distal limbs and skin necrosis	Used for catecholamine refractory vasodilatory shock Only in central line
Milrinone (PDE III inhibitor)[26,27,28,29]	Phosphodiesterase inhibitor Increases intracellular cAMP Inotropy, lusitropy. Vasodilatation - reduction in preload and afterload Improves SvO_2 70% bound to plasma proteins, with approximately 85% renal elimination T1/2- 20 minutes in healthy children Increases in renal or cardiac dysfunction May increase to 1.5 hours in septic shock	Used to increase in septic shock cardiac contractility following cardiac surgery Role in improving perfusion in patients with “cold shock” Vasodilator property-may be useful in the setting of pulmonary hypertension	Good safety profile	Compared with dobutamine, milrinone produces a greater reduction in SVR for a given degree of improvement in inotropic state. BP is well maintained, even in the face of reduced SVR, because of the associated improvement in contractility and stroke volume

Drug	Clinical pharmacology / Pharmacokinetics	Clinical role	Adverse effects	Practical consideration
Levosimendan [30,31]	Myofilament calcium sensitizer and a novel inotrope that increases contractility without increasing cAMPlevels appreciably at clinically recommended doses Unlike other inotropes, levosimendan does not exert its action through potentially harmful increases in intracellular Ca2+. This may explain why this agent does not impair diastolic relaxation and cardiac rhythm and has less harmful effects on myocardial energetics T1/2- 96 hours	Cardiovascular effects- increase in HRVasculature-vasodilator by decreasing the sensitivity of myofilaments to Ca2+ and activating of K+ channels	Use in Pediatric population is not established	
Digoxin[33]	Glycosides bind to and inhibit sodium-potassium ATPase which produces an increase in intracellular calcium and enhances the inotropic state of the myocardium		Dysrrhythmias, nausea, vomiting, anorexia, diarrhea, constipation, abdominal pain and abdominal distension Visual disturbances, photophobia, headache, muscle weakness, fatigue, drowsiness, dizziness, vertigo, seizures and neuropsychiatric abnormalities	It is an effective inotropic agent having desirable property of slowing. As a result of its narrow therapeutic window, long half-life and the emergence of newer medications, the role of digoxin in the acute setting has diminished

Table IV summarises the common method of preparing infusion and normal range of dosing of various inotropes.

Table IV. Dosage and preparation of common drugs

Drugs	Preparation	Infusion rate and max dose	Usual dose range (μg/kg/min)
Epinephrine Norepinephrine	0.15mg × body weight (kg), added to diluent to make 25 mL	1 mL/hr = 0.1 μg/kg/min	0.05 to 0.3
Dopamine Dobutamine	15mg × body weight (kg), added to diluent to make 25 mL	1 mL/hr = 1 μg/kg/min	5 to 20
Milrinone	0.75× body weight (kg), added to diluent to make 25 mL	1ml/hr = 0.5 μg/kg/min	0.25 to 0.75
Vasopressin	0.75 × body weight (kg) units, added to diluent to make 25 mL	1 ml/hr = 0.0005 U/kg/min	0.0001 to 0.002 U/kg/min

Table V. Summary for selection of appropriate agent as per physiology

Hemodynamic pattern	Blood pressure		SVR
	Normal	Decreased	Increased
Septic shock Stroke index ↑ or ↔		Norepinephrine	
Stroke index ↓	Dopamine or Dobutamine	Dopamine or Epinephrine (or Dobutamine + Norepinephrine)	Dobutamine + Vasodilator and/or PDIII inhibitor
Cardiogenic shock	PD III inhibitor or Dobutamine or Dopamine	Epinephrine or Dopamine	Dobutamine + Vasodilator and/or PDIII inhibitor
Myocardial dysfunction (complicating critical illness)	PD III inhibitor or Dobutamine or Dopamine	Epinephrine or Dopamine	Dobutamine + Vasodilator and/or PDIII inhibitor
Congestive heart failure	PD III inhibitor or Dobutamine or Dopamine		Dobutamine + Vasodilator and/or PDIII inhibitor
Bradycardia		Isoproterenol	

For infants with fluid-refractory, hypotensive septic shock, vasoactive therapy with either an epinephrine infusion or norepinephrine infusion is preferred rather than a dopamine infusion.[34] This recommendation was based on the findings of two small, randomized controlled trials in children with fluid-refractory septic shock, which demonstrate improved survival with initiation and titration of epinephrine compared with dopamine.[35,36] Epinephrine is preferred in children with signs of myocardial dysfunction, and norepinephrine is used in those with signs of low systemic vascular resistance or vasodilation (SVR) (Table V).

For shock refractory to treatment with dopamine hydrochloride, if cardiac output is high and peripheral vascular resistance is low, noradrenaline/norepinephrine should be added[3] or if cardiac output is low and peripheral vascular resistance is high, adrenaline/epinephrine should be added[37] (Table V). Additionally, in cold shock, with normal cardiac index and elevated SVR a vasodilator such as glyceryl trinitrate, or sodium nitroprusside can be used (Table V).

If the shock is resistant to volume expansion and catecholamines, and there is suspected or proven adrenal insufficiency, low dose hydrocortisone can be used. However studies have not shown conclusive results for the same.[38,39] Alternatively, if the child is resistant to catecholamine, and vascular resistance is low, vasopressin can be added.

In cardiogenic shock, the aim is to improve cardiac output and to reduce the afterload on the heart. If central venous pressure is low, cautious volume expansion with a colloid or crystalloid can be used. An inotrope such as adrenaline/epinephrine or dopamine hydrochloride should be given to increase cardiac output. Dobutamine is a peripheral vasodilator and is an alternative if hypotension is not significant. Milrinone has both inotropic, lusitropic and vasodilatory effects and can be used when vascular resistance is high. Alternatively, glyceryl trinitrate or sodium nitroprusside can be used to reduce vasoconstriction.[40]

The use of sympathomimetic inotropes and vasoconstrictors should preferably be confined to the intensive care setting and undertaken with invasive haemodynamic monitoring.

Vasoconstrictor sympathomimetics/vaso-constrictors

Vasoconstrictor sympathomimetics raise blood pressure transiently by acting on alpha-adrenergic receptors to constrict peripheral vessels. They are sometimes used as an emergency method of elevating blood pressure where other measures have failed. The danger of vasoconstrictors is that although they raise blood pressure they also reduce perfusion of vital organs such as the kidney and increase afterload.

Ephedrine hydrochloride is used to reverse hypotension caused by spinal and epidural anaesthesia.[41]

Metaraminol is used as a vasopressor during surgery or critical illness to reverse short-term episodes of hypotension.[3] Phenylephrine hydrochloride causes peripheral vasoconstriction and increases arterial pressure.

Ephedrine hydrochloride, metaraminol and phenylephrine hydrochloride are rarely needed in children and should be used under specialist supervision.

Noradrenaline/norepinephrine is reserved for children with low systemic vascular resistance that is unresponsive to fluid resuscitation following septic shock, spinal shock, and anaphylaxis.

Adrenaline/epinephrine is mainly used for its inotropic action. Low doses (acting on beta receptors) cause systemic and pulmonary vasodilation, with some increase in heart rate and stroke volume and also an increase in contractility; high doses act predominantly on alpha receptors causing intense systemic vasoconstriction (Table III).

Conclusion

Inotropes are one of the most commonly used drugs in intensive care settings. Surprising that despite being administered for many years, there are very few guidelines for their use. The key to proper use of inotropes is to first understand what each drug does, then to choose those that fit the clinical problem the given child has and lastly to set up monitoring for the patient so they get the right amount of the right agent. Inotropes are drugs with multiple effects and adverse reactions and should only be used if the intensivist and the rest of the team are aware of the effects of each drug and are prepared to deal with the side effects.

Points to Remember

- ***Inotropes are one of the most commonly used drugs in intensive care setting, which increases myocardial contractility and have variable effects on peripheral vascular resistance.***
- ***The various classes of drugs include catecholamines, bipyridines, vasopressors, glycosides, Ca sensitizer, afterload reducing agents and sympathomimetics.***
- ***Selection of appropriate drug is based on the hemodynamic state, blood pressure and systemic vascular resistance.***
- ***They have multiple effects and should be used carefully.***
- ***One must know the adverse effects and be prepared to deal with side effects.***

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ADOLESCENCE

ADOLESCENT SLEEP PROBLEMS

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Abstract: *Sleep is a universal process in all species. In adolescents due to heightened activity and fulfilling academic needs, the quantity and quality of sleep is getting affected. Chronic lack of sleep is causing deleterious effect on holistic health of adolescents. Pediatricians should advice all adolescents on sleep hygiene during routine health visits and screen for sleep related problems so that appropriate management can be initiated before it manifests into a sleep disorder. Sleep disorders require detailed evaluation and treatment.*

Keywords: *Adolescent sleep hygiene, Sleep quality, Adolescent sleep disorders.*

Sleep is integral to the health and survival of human beings. Adequate quantity and quality of sleep rejuvenates, restores and maintains the optimal functioning of the body. About 8 to 10 hours of daily sleep is needed for every adolescent to be in good health.[1] Using pooled mean estimates, it has been calculated that globally, adolescents between 12-17 years of age sleep for 7 hours in the night on school days.[2] When adolescents are allowed to sleep, they slept for almost 9.25 hours in a study conducted yearly from the age of 10-12 years till 15-18 years of age with no relation to age and stage of pubertal maturation, Ohayon et al., showed that on school days there is reduced duration of sleep with no change on leave days, reduced sleep duration on school days is dependent on environmental demands.[3] Study from urban region of Kerala suggests 60% of the adolescents were sleeping for a period of <8 hours with a mean duration of 7.2 ± 1.26 hour.[4] Another study from Delhi found that the preteens had better sleep compared to teens.[5] A community study from Tamil Nadu revealed that over 64% of adolescents sleep <8 hours at night and 5.6% sleep <6 hours.[6]

Due to the pandemic related lockdown and online schooling many adolescents reported better quality, quantity of sleep with less daytime sleepiness. Also, there is a delay in the onset of sleep and wake time.[7] Mostly the preparation needed to attend online classes were less and allowed them to get few extra hours of sleep. However, there is increase in the incidence of anxiety/ depression and media/gadgets use.

Factors affecting sleep in adolescence

Sleep regulation has two basic processes acting concurrently that control sleep and wakefulness. As the child grows into adolescence, duration of sleep hours gets reduced. During puberty there is a slow change in the bedtime and wake time due to circadian sleep rhythm shift. There are various factors which affect sleep. Internal factors are puberty related shift in biological clock resulting in delayed bed time/wake time and decreased internal drive to sleep.[8] External factors known to interfere with adolescent sleep are early school hours, after school activities, high ambient temperature, poor exposure to sunlight, vigorous exercise and emotional confrontations before bed time, academic pressure, caffeine intake, alcohol and drug use, anxiety, depression, allergic rhinitis, chronic adenoid hypertrophy, anomalies of the airway, chronic diseases like asthma, obesity, psychological trauma and too much screentime.[9-11] In adolescence, lack of sleep is attributed to various physical and mental changes occurring during this period and shift of circadian sleep rhythm. The adolescents tend to sleep for longer duration during holidays to compensate for inadequate sleep during school days that further disturbs the circadian rhythm and results in poor sleep.The protective factors, such as parent set bedtimes and good sleep practices, decline as adolescents grow older.[12] Moreover, sleep competes with increasing school demands and the pervasive use of information and communication technology (ICT). In the Tamil Nadu study 43% adolescents had disturbed sleep, 64% watched television and 23% used mobile phones in bed before

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sleeping.[6] Using screens at bedtime impair sleep because of physiological arousal, increasing alertness and engagement which results in the delay of secretion of melatonin due to the blue light emitted from the devices.[13]

Importance of sleep

In adolescents sleep is needed to maintain various physical, mental/emotional health and vital brain functions like attention, memory, thinking, learning new skills and self-regulation. During sleep, growth hormone, testosterone, cortisol, ghrelin, leptin and insulin are secreted and immune regulation takes place. The process of pruning or synaptic reorganization which is maximum in adolescent period is responsible for maturation of sleep architecture.[14]

Box 1. Effects of insufficient sleep

- Morning tiredness: Negative effects on cognitive function, mood and motivation
- Day sleepiness: Delay in sleep onset in adolescents has been associated with fatigue, mood disorders and anxiety
- Classroom inattentiveness, difficulty in learning an instrument or any new skill
- Obesity, diabetes mellitus
- Road traffic accidents
- Impulsive behaviour, anger, aggression, violence
- Immune dysregulation
- Suicidal behaviour

Effects of insufficient sleep in adolescents is given in Box 1. Lack of sleep is linked with higher occurrence of overweight and obesity[15,16] and an increased risk of prehypertension and hypertension independent of obesity putting these children at risk for long term cardiovascular morbidity.[16,17] In a recent study from Mumbai, it was reported that less than 7 hours of sleep and a poor quality of sleep-in adolescents was a risk factor for obesity. It was also seen that there was a clustering of risk factors in 18.8% adolescents in terms of physical inactivity, increased screen time and poor sleep leading to obesity.[18]

Sleep disorders

Many studies show various problems related to duration of sleep, quality of sleep, patterns and sleep lag.[19] Bedtime autonomy increases and adolescents have more autonomy also in their evening activities.[20]

When an adolescent with delayed sleep-wake phase disorder (DSPD) is allowed to sleep at will, a normal

Table I. Common sleep disorders in adolescents

Psychophysiological insomnia (PI)	Difficulty in getting sleep or to stay in that state due to preoccupation with several thoughts leading to anxiety and stress during night
Delayed sleep-wake phase disorder (DSPD)	A delay in circadian physiology during adolescence can result in inability to sleep with delayed wake up time called as -Night owl
Obstructive sleep apnea (OSA)	Usually associated with obesity. ENT causes of upper airway obstructions
Narcolepsy	Recurrent episodes of excessive daytime sleepiness with significant functional impairment
Restless leg syndrome	Uncontrollable desire to move legs, urge to move along with uneasiness in lower limbs. Bedtime struggles and difficulty in falling asleep. Usually, manifestations start towards the end of the day, rest makes it worse, improves with limb movement
Sleep walking (Somnambulism)	Seen 1-2 hours after sleeping. Getting out of bed, and walking around with open eyes. It is difficult to wake them during the episode, with a short period of disorientation / confusion if awakened. No memory of the episode next morning
Excessive day time sleepiness	Feeling of sleepiness or easily falling asleep during daytime. Manifests as lethargy or moodiness, lack of interest and motivation, feelings of boredom, depression. Poor academic or sports performance. Feels sleepy during class or while doing homework. Puberty related sleep phase delay, use of media – mobile, television, video games and internet compete with sleep time

Box 2. Details in typical sleep diary

Bedtime and/or lights-out time

Wake-up time

How long it takes to fall asleep

The number and duration of sleep interruptions

The number and duration of daytime naps

Perceived sleep quality

Consumption of chocolate, caffeine and/or tobacco

Daily medications

Daily exercise

quantity and quality of sleep is observed. DSPD occurs whenever the affected individual sleeps at odd hours as per social demands. In adolescents'prevalence is as high as 14%.[21]

Assessment of sleep related issues

This includes detailed history taking from parents and adolescents separately in privacy offering confidentiality. Sleep and media history forms a part of 'activities' section of HEEADSSS psychosocial history taking. This is a clinical tool for screening for traumatic life events, scholastic and non-scholastic stressors, anxiety, depression, suicidality, aggression and safety issues. On examination,

Table II. BEARS Sleep Screening

	Toddler / Preschool child (2-5 years)	School-Aged child (6-12 years)	Adolescent (13-18 years)
Bedtime Problems	Does your child have any problems going to bed? or falling asleep?	Does your child have any problems at bed time? (P)	Do you have any problems falling asleep at bedtime? (C)
Excessive daytime Sleepiness	Does your child seem over tired or sleepy a lot during the day?	Do you have any problems going to bed?	Do you feel sleepy a lot during the day? in school? while driving? (C)
	Does she still take naps?	Does your child have difficulty waking in the morning, seem sleepy during the day or take naps? (P)	Do you feel tired a lot? (C) Do you wake up a lot at night? Have trouble getting back to sleep? (C)
Awakenings during the night	Does your child wake up a lot at night?	Does your child seem to wakeup a lot at night? Any sleepwalking or nightmares? (P)	What time do you go to bed and get upon school days? Weekends?
		Do you wake up a lot at night? Have trouble getting back to sleep? (C)	How much sleep do you usually get? (C)
Regularity and duration of sleep	Does your child have a regular bed time and wake time?	What time does your child go to bed and get upon school days? weekends? What time do you usually go to bed on school nights?? Do you think he/she is getting enough sleep? (P)	Does your teenager snore loudly or nightly? (P)
	What are they?	Does your child have loud or nightly snoring or any breathing difficulties at night? (P)	
Sleep-disordered breathing	Does your child snore a lot or have difficulty breathing at night?		

(P) Parent, (C) Child

evaluation of chronic medical disorders like obesity, asthma, obstructive sleep apnea syndrome (OSAS) and hypertension is essential. The following history should be elicited in detail:

- Sleep behaviour (sleep time, falling asleep and awake times).
- Bed type, sharing with others, surrounding light and sound, temperature, routine around the sleep time
- Household structure, daily routines, and cultural practices may be important in influencing the timing and ease of sleep (e.g. parental work patterns, evening activities, number of household members).
- Dietary practices that influence sleep, including timing of meals and caffeine intake.
- Assess symptoms of OSA (e.g. gasps, snoring noises, breathing pauses, etc.) in all children who snore regularly.
- Sleep diary is important when the diagnosis cannot be made with history. Details of sleep diary is given in Box 2.

The common sleep disorders seen are given in Table I.

The following sleep screening tools are available:

1. BEARS sleep screening
2. The Pittsburgh Sleep Quality Index (PSQI)
3. Adolescent Sleep Hygiene Scale revised (ASHSr)

BEARS sleep screening tool is simple to use in office practice[22] provided in Table II.

BEARS sleep screening tool BEARS is divided into 5 major sleep domains (B=Bedtime issues, E=Excessive daytime sleepiness, A=Night awakenings, R=Regularity and duration of sleep, S=Snoring) and helps clinicians evaluate potential sleep problems in children 2 to 18 years old. Each sleep domain has a set of age-appropriate "trigger questions" for use in the clinical interview.

Different ways to assess sleep are self-reports, actigraphy, and polysomnography (PSG). Assessment of perceived sleep difficulties and daytime functioning are easier with self-reports and it is also used in diagnosis of few psychiatric conditions.[23]Actigraphy device worn like a wristwatch differentiates movements during sleep and while awake. It can measure duration of sleep with night awake period. It can provide sleep pattern over long periods of time like few weeks to months. Polysomnography (PSG) needs concurrent tracings of electroencephalogram (EEG),

Box 3. Treatment of DSPD

1. At least half hour prior to the planned bedtime bright lights should be avoided
2. Sleep time needs to be shifted earlier; keep shifting 15-20 min early everyday
3. Smaller doses of melatonin (0.5mg to 1mg can be considered. It must be taken 4-6 hours prior to the current bedtime
4. Try to get an early morning sunlight; exposure to morning light helps in shifting circadian sleep rhythm to earlier time
5. Schedule same work all through the week for sleep time as well as wake time

The International Classification of Sleep Disorders: Diagnostic and Coding Manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.

Box 4. Basic principles of sleep hygiene

- Wake up and bedtime should be at the same time daily even on non-school days
- To catch up lost sleep, do not sleep on weekends
- Daytime naps should be short, less than 1hour (those with problems falling asleep at night should avoid napping) and early to mid-afternoon is ideal
- Spend time outside daily. Exposure to sunlight keeps circadian rhythm on check
- Regular exercise
- Bed must be used only for sleeping. The bedroom should have an ambient cool temperature
- Involve in relaxing, and enjoyable activities half to one hour before sleep time. Do not indulge in vigorous exercise or arguments
- One hour prior to bedtime do not engage in watching television or digital devices. Bedroom should be a media free zone
- Eat regular meals and do not go to bed hungry
- Avoid eating or drinking caffeine containing products like cocoa beverages, coffee or chocolates
- Do not consume alcohol and do not smoke
- Avoid using sleeping pills, melatonin or other sleep aids unless prescribed by doctor. These can be dangerous and the sleep problems often return when one stops taking the medicine

electrooculogram (EOG) and electromyogram (EMG). It records total duration of sleep, sleep lag, awaking and movement of limbs.

Management

Sleep hygiene and screen time guidelines should be advised by all pediatricians catering to adolescents. Evaluation of sleep related issues must include use of any of the scales mentioned above. If sleep disorders are detected, then appropriate therapy needs to be given as mentioned below. Iron deficiency can be responsible for restless leg syndrome (Iron supplementation if serum ferritin <50mg/dL). Appropriate treatment of ENT causes responsible for OSA should be provided.

Treatment of DSPD is given in Box 3.

Stress management and relaxation techniques along with life skills education should be imparted to adolescents with mental distress. Co-morbidities like obesity and hypertension should be managed according to standard clinical guidelines. Psychiatric issues should be managed appropriately by psychotherapy, psychopharmacology and referral to mental health professional, if required. As a step towards maintaining good quality and quantity of sleep, it is advisable for later school start time for middle and high school.

Sleep hygiene for adolescents

Few basic principles for healthy sleep for adolescents are provided in (Box 4).

Conclusion

Pediatricians need to stress on good sleep hygiene and provide anticipatory guidance to children, adolescents and parents. It is important to screen for various sleep disorders and the comorbidities associated with unhealthy sleep patterns in office practice so that early interventions can be planned for better results.

Points to Remember

- ***Good quality and quantity of sleep forms the core for optimal functioning of an adolescent.***
- ***Pediatricians should advice about sleep hygiene.***
- ***BEARS sleep screening tool can be used in office practice.***
- ***Adolescents with serious sleeping disorder need tailored therapy.***
- ***Parents should be educated about instilling sleep hygiene from early childhood which needs to continue into adolescent life and thereafter.***

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CLIPPINGS

Perceptions and experiences of healthcare workers during the COVID-19 pandemic in the UK

The COVID-19 pandemic has set unprecedented demand on the healthcare workforce around the world. The UK has been one of the most affected countries in Europe. The aim of this study was to explore the perceptions and experiences of healthcare workers (HCWs) in relation to Covid-19 and care delivery models implemented to deal with the pandemic in the UK. The study was designed as a rapid appraisal combining: (1) a review of UK healthcare policies (n=35 policies), (2) mass media and social media analysis of front-line staff experiences and perceptions (n=101 newspaper articles, n=1 46000 posts) and (3) in-depth (telephone) interviews with front-line staff (n=30 interviews). The findings from all streams were analysed using framework analysis. RESULTS: Limited personal protective equipment (PPE) and lack of routine testing created anxiety and distress and had a tangible impact on the workforce. When PPE was available, incorrect size and overheating complicated routine work. Lack of training for redeployed staff and the failure to consider the skills of redeployed staff for new areas were identified as problems. Positive aspects of daily work reported by HCWs included solidarity between colleagues, the establishment of well-being support structures and feeling valued by society. Study highlighted the importance of taking into consideration the experiences and concerns of front-line staff during a pandemic. Staff working in the UK during the COVID-19 pandemic advocated clear and consistent guidelines, streamlined testing of HCWs, administration of PPE and acknowledgement of the effects of PPE on routine practice

Perceptions and experiences of healthcare workers during the COVID-19 pandemic in the UK Vindrola-Padros C, Andrews L, Dowrick A, Djellouli N, Fillmore H, Bautista Gonzalez E. BMJ Open https://pubmed.ncbi.nlm.nih.gov/33154060.

CASE REPORT

AN UNUSUAL CAUSE OF LIMP

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Abstract: *Syringomyelia, though unusual, should be considered in the differential diagnosis of a limping child. This condition is a close mimicker of several other neurological and muscular disorders. Due to its slow progression and symptomatic resemblance to various other more common conditions, diagnosis is often delayed. A negative family history, certain precipitating events, signs and symptoms; and appropriate neuro-imaging clinches the diagnosis. It is important to diagnose syringomyelia early in the course of the disease so as to follow it up regularly and intervene timely to prevent permanent neurological sequelae. A five years old child with syringomyelia as an unusual cause of limping is presented here.*

Keywords: *Syringomyelia, Syrinx, Idiopathic, Secondary.*

Syringomyelia is a rare neurological disorder. An incidence of 8.4 cases per 1,00,000 has been reported in pediatric population.[1,2] This is a chronic, slowly progressive condition.[3] A fluid-filled cavity known as "syrinx" develops within the spinal cord which contains a derivative of CSF (cerebrospinal fluid)[4] and expands over time, causing compression or destruction of the surrounding neural structures. Child with limping gait, a case of syringomyelia is presented here.

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Case Report

A five years old, male child, hailing from Western Odisha, presented with complaints of limping since he started walking. No preceding history of gluteal injection, trauma, blood transfusion or contact with tuberculosis. He was born to non-consanguineous parents and had an uneventful perinatal history, delivered at term via normal vaginal delivery with birth weight of 2.5 kg and cried immediately after birth. He needed NICU admission for management of neonatal sepsis and prolonged stay for 22 days, details of which were not evident. His developmental milestones were normal except delayed walking. There was no similar illness in the family. He had a normal elder sibling.

His examination was remarkable for a normal facies and absence of neurocutaneous markers. He had scoliosis with contractures (right tendo-achilles> left) and callosities in both lower limbs. Both lower limbs were externally rotated and abducted while supine. Neurological examination revealed mild hypertrophy of both calf muscles (right>left), mild spasticity and a power of 4/5 in both lower limbs around all joints with absent knee jerks, preservation of ankle jerks and positive Babinski sign. He also had truncal weakness but normal neck power. He had a waddling gait and positive Gower's sign. Higher functions, cranial nerves and sensory system were normal and there were no cerebellar or extrapyramidal signs.

Clinical possibilities of congenital spinal malformation, spastic diplegia due to a perinatal insult, hereditary spastic paraparesis and inherited metabolic disorders were considered. In view of combination of a proximal muscle (hip girdle) weakness and upper motor neuron (UMN) signs, central nervous system (CNS) disease co-existing with peripheral nervous system (PNS) involvement was considered.

Investigations revealed an unremarkable complete blood count with peripheral smear, serum creatine phosphokinase (CPK), Vitamin B12 and folate levels. Thyroid profile revealed hypothyroidism (TSH of 10.953 microIU/ml with free T4 in low normal range) for which he was started on oral thyroxine supplementation.

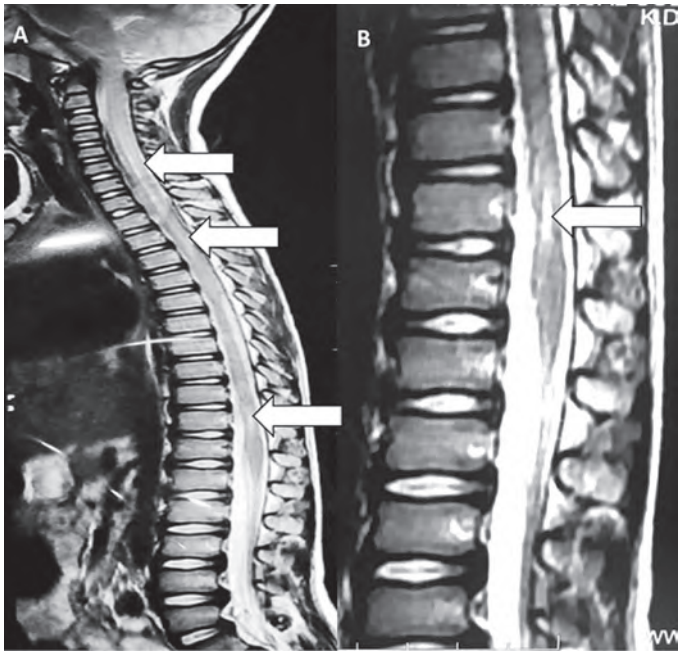

Fig.1. MRI

A: T2 Sagittal view of the spinal cord showing a distended fluid filled (as bright as CSF) linear cavity (arrows) between C4 and T11 levels. The physiological central canal is either not appreciable or is visible as a thin fluid column.

B: A close-up image of the terminal portion of the cord demonstrating the syrinx (arrow) clearly.

There was vitamin D insufficiency (25-OH-Vit D of 16.94 ng/ml) with normal calcium and alkaline phosphatase (ALP) levels.

Nerve conduction velocity (NCV) was normal. Neuro-imaging was planned. MRI of whole spine revealed long segment intra-medullary T2 hyperintensity (likely syrinx) extending from C4 vertebral body level to D11 vertebral body level (Fig.1). MRI of the brain was normal. A final diagnosis of syringomyelia (C4 to D11) with scoliosis, hypothyroidism and vit D insufficiency was made. The syringomyelia in our case may be secondary to the eventful neonatal period (probably, neonatal meningitis resulting in NICU stay of 22 days).

A neurosurgical opinion was taken and it was decided to keep him under regular follow up. Annual neuroimaging of the child was recommended to monitor the progression of syringomyelia and plan for decompression and shunt placement whenever symptoms worsened. In view of bilateral lower limb contractures, physiotherapy was started and tendo achilles (TA) release surgery planned after 4 weeks of physiotherapy.

Discussion

Syringomyelia is a rare neurological disorder. The etiology remains unclear till date; some of them being idiopathic, while the remaining are secondary to CNS infections, tumors or trauma. Several theories have been postulated to describe its pathophysiology, including the cerebellar piston theory, intramedullary pulse pressure theory and increased spinal subarachnoid pressure.[5]

The average age of diagnosis of syringomyelia is 10 years.[6] The type, size and exact location of the syrinx dictates the clinical presentation. Syringomyelia can present with a myriad of clinical signs and symptoms - muscle weakness, pain along with stiffness in the legs, muscle contractures, reduced temperature sensation, neck or shoulder pain or ataxia. 25-85% of cases of syringomyelia have scoliosis,[2,4,7-9] which may be the only presenting complaint. It is important to identify associated malformations including meningomyelocele, hydrocephalus and Arnold Chiari malformation.

It is important to note that syringomyelia can present with a combination of upper and lower motor neuron signs and symptoms, which sometimes makes the diagnosis difficult for the clinician. The most common presenting symptom in children is pain, followed by paresthesias, numbness and unnoticed hand injuries, followed by weakness and wasting, but long tract signs can also occur.[10]

The treatment is often symptomatic and tailored to the individual case. A multi-disciplinary approach with a team consisting of a pediatrician, a neurologist, a neuro surgeon and a physiotherapist is essential. Specific neuro surgical intervention is only required in case of disease progression, presence of certain life-threatening symptoms or debilitating symptoms severely affecting the quality of life. Various decompressive strategies including laminectomy, lysis of adhesions and cranio cervical decompression have been used based on the etiology. Syringo-subarachnoid shunting is helpful in patients with progressive neurological symptoms.[2]

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CLIPPINGS

Difficulties Encountered While Using PPE Kits and How to Overcome Them: an Indian Perspective Cureus (https://pubmed.ncbi.nlm.nih.gov/33251079)

After a slow start due to an effective lockdown, the coronavirus disease 2019 (COVID-19) pandemic in India has been raging at a rapid pace, posing a formidable challenge to the healthcare system in the country. The personal protective equipment (PPE) undoubtedly provides a shield of protection for the healthcare workers (HCWs) fighting the disease as a valuable asset to the nation. However, there have been various problems associated with the PPE, ranging from its shortage to problems arising from heat, dehydration, etc while wearing them. There is a need to assess these problems faced by HCWs both qualitatively and quantitatively for their timely and effective redressal. An electronic questionnaire survey was conducted among a cohort of HCWs who had performed COVID-19 duties and used PPE kits. The cohort consisted of different categories of doctors, nursing personnel, and other paramedical staff. The most common problems associated with using PPE kits was excessive sweating (100%), fogging of goggles, spectacles, or face shields (88%), suffocation (83%), breathlessness (61%), fatigue (75%), headache due to prolonged use (28%), and pressure marks on the skin at one or more areas on repeated use (19%). Occasional problems reported were skin allergy/dermatitis caused by the synthetic material of the PPE kit, face shield impinging onto the neck during intubation, and nasal pain, pain at the root of the pinna, and slipperiness of shoe covers. Various ways and means have been employed by the HCWs to actively address and solve these problems. These plausible solutions will definitely help the HCWs to deal with and solve the problems arising out of the PPE use.

Agarwal A, Agarwal S, Motiani P. Difficulties Encountered While Using PPE Kits and How to Overcome Them: An Indian Perspective Cureus 2020 Nov; 12(11): e11652. Published online 2020 Nov 23. doi: 10.7759/cureus.11652.

Delayed production of neutralizing antibodies correlates with fatal COVID-19

Recent studies have provided insights into innate and adaptive immune dynamics in coronavirus disease 2019 (COVID-19). However, the exact features of antibody responses that govern COVID-19 disease outcomes remain unclear. In this study, we analyzed humoral immune responses in 229 patients with asymptomatic, mild, moderate and severe COVID-19 over time to probe the nature of antibody responses in disease severity and mortality. We observed a correlation between anti-spike (S) immunoglobulin G (IgG) levels, length of hospitalization and clinical parameters associated with worse clinical progression. Although high anti-S IgG levels correlated with worse disease severity, such correlation was time dependent. Deceased patients did not have higher overall humoral response than discharged patients. However, they mounted a robust, yet delayed, response, measured by anti-S, anti-receptor-binding domain IgG and neutralizing antibody (NAb) levels compared to survivors. Delayed seroconversion kinetics correlated with impaired viral control in deceased patients. Finally, although sera from 85% of patients displayed some neutralization capacity during their disease course, NAb generation before 14 d of disease onset emerged as a key factor for recovery. These data indicate that COVID-19 mortality does not correlate with the cross-sectional antiviral antibody levels per se but, rather, with the delayed kinetics of NAb production

Lucas C, Klein J, Sundaram ME, Liu F, Wong P, Silva J, et al. Delayed production of neutralizing antibodies correlates with fatal COVID-19. Nat Med 2021 Jul;27(7):1178-1186. doi: 10.1038/s41591-021-01355-0. Epub 2021 May 5.

CASE REPORT

ACCIDENTAL INGESTION OF MINOXIDIL

***Sanjana R**
***Abinaya S**
****Suresh Kannan K**

Abstract: *Minoxidil, a potassium channel opener acts as a potent vasodilator. Nowadays it is widely used as a topical applicant in androgenic alopecia. A very few cases of poisoning due to topical minoxidil ingestion are reported in literature. We encountered a child who developed inotrope responsive shock following accidental ingestion of the topical minoxidil solution.*

Keywords: *Minoxidil, Ionotrope responsive shock, Noradrenaline, Dopamine.*

Minoxidil, a potassium channel opener acts as a potent vasodilator. Nowadays it is widely used as a topical applicant in androgenic alopecia.[1] A very few cases of poisoning due to topical minoxidil ingestion are reported in literature. We encountered a child who developed inotrope responsive shock following accidental ingestion of the topical minoxidil solution.

Case Report

A 3 year old developmentally normal female child with no comorbidities presented with vomiting since 4 hours. She had accidentally consumed approximately 5 mL of 5% topical solution of minoxidil.

On arrival to the hospital, she was in hypotensive, vasodilatory shock. The child was lethargic, voice responsive, afebrile; had tachycardia (140/min), weak pulse and hypotension with wide pulse pressure, BP 70/30 mm Hg. CVS examination revealed no gallop or murmur. Respiratory rate of 50/min, no increase in work of breathing. Pupils normal in size and reacting to light equally. Fundus examination was normal. ECG showed sinus rhythm with no significant ST-T changes.

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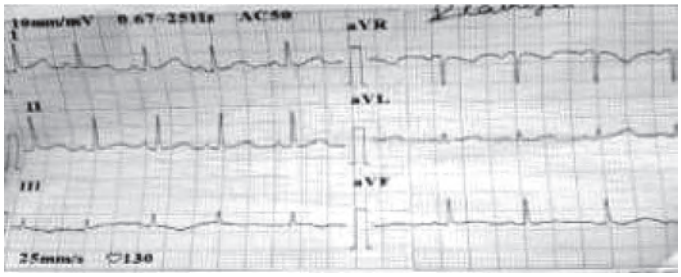

Fig.1. ECG showing sinus rhythm

The child was started on oxygen support through non re-breathing mask (NRM). Three boluses of 20 mL/kg of normal saline rapid infusion were given. The child's systolic blood pressure improved but the diastolic BP remained low and SpO_2 measured 96%. The child was started on noradrenaline infusion.

After 24 hours, systolic blood pressure also dropped. Additional inotrope support dopamine was started along with noradrenaline.

Investigations showed normal renal and liver functions. Serial ECG had no significant changes (Fig.1). Chest X-ray was normal. Cardiac enzymes were normal. Echo showed good contractility.

She was on inotrope support for 3 days. As the child showed improvement inotropes were gradually tapered (noradrenaline followed by dopamine).

Discussion

This is the first case of accidental ingestion of topical minoxidil, which we encountered, presenting with fluid refractory shock. Minoxidil has 95% gastrointestinal absorption and peak serum concentration is reached in one hour of ingestion. Minoxidil does not bind to plasma proteins and its volume of distribution is high. It has a plasma $t_{1/2}$ of 3-4 hours, but its duration of action is 24 hours or occasionally even longer. This is due to the active metabolite minoxidil sulfate which directly activates the K^+ ATPase channel.[2] The opened potassium channels cause K^+ efflux (hyperpolarisation) causing smooth muscle relaxation resulting in arteriolar dilatation. Thus the active metabolite causes delayed hypotensive effects.[3] Minoxidil and minoxidil - o- glucuronide have shorter half lives and do not explain these prolonged hypotensive effects.

The cardiac consequences due to the baroreceptor-mediated activation of the sympathetic nervous system during minoxidil therapy are an increase in heart rate, myocardial contractility and myocardial O_2 consumption. Thus, myocardial ischemia can be induced by minoxidil.[4]

In our case, the patient ingested about 5 mL of the 5% solution, equivalent to 250 mg minoxidil, which is a toxic dose. Since the child presented after 4 hours, gastric lavage was not done. The child required crystalloids and double vasopressor support.[5] Dopamine improved the cardiac output and blood pressure. Noradrenaline also provided a control over the blood pressure. She received the inotrope support for first 3 days and was gradually weaned. Pulmonary edema and papilledma[6] are rare and were not present in the index case.

Literature on minoxidil poisoning is scarce. Isles, et al. Reported a 2-year-old boy who allegedly ingested 100 mg minoxidil and presented to the emergency department an hour after ingestion with tachycardia of 160/min as the only symptom, managed by induction of emesis, gastric lavage and observation.[7]

The exploratory nature of of our toddler patient and the presence of the drug in an attractive container within the reach of the child has probably aided in its consumption. The measurement of serum levels of minoxidil would have strengthened our report, but minoxidil is not detectable in the routinely performed toxic screen analysis in our hospital.

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CLIPPINGS

The interactive effects of ambient air pollutants-meteorological factors on confirmed cases of COVID-19 in 120 Chinese cities

Emerging evidence has confirmed meteorological factors and air pollutants affect novel coronavirus disease 2019 (COVID-19). However, no studies to date have considered the impact of interactions between meteorological factors and air pollutants on COVID-19 transmission. This study explores the association between ambient air pollutants (PM2.5, NO2, SO2, CO, and O3), meteorological factors (average temperature, diurnal temperature range, relative humidity, wind velocity, air pressure, precipitation, and hours of sunshine), and their interaction on confirmed case counts of COVID-19 in 120 Chinese cities. Investigators modeled total confirmed cases of COVID-19 as the dependent variable with meteorological factors, air pollutants, and their interactions as the independent variables. To account for potential migration effects, we included the migration scale index (MSI) from Wuhan to each of the 120 cities included in the model, using data from 15 Jan. to 18 Mar. 2020. As an important confounding factor, MSI was considered in a negative binomial regression analysis. Positive associations were found between the number of confirmed cases of COVID-19 and CO, PM2.5, relative humidity, and O3, with and without MSI-adjustment. Negative associations were also found for SO2 and wind velocity both with and without controlling for population migration. In addition, air pollutants and meteorological factors had interactive effects on COVID-19 after controlling for MSI. In conclusion, air pollutants, meteorological factors, and their interactions all affect COVID-19 cases.

The interactive effects of ambient air pollutants-meteorological factors on confirmed cases of COVID-19 in 120 Chinese cities. Zhou J, Qin L, Meng X, Liu N.Environmental Science and Pollution Research International https://pubmed.ncbi.nlm.nih.gov/33501581.

CASE REPORT

TYPHOID FEVER WITH UNUSUAL COMPLICATIONS

***Satheesh C**
****Mahesh N**
*****Saravanan M**
******Jayakumar Reddy**

Abstract: *Typhoid fever is known to medical professionals from time immemorial. Our forefathers in medicine faced complications in patients with typhoid fever during pre-chloramphenicol era. MDR S. Typhi was a challenge till the treatment protocol was revisited with third generation cephalosporins, macrolides and quinolones. Despite these advances it appears that typhoid fever cannot be taken for granted. We are reporting a challenging case of typhoid fever with intestinal complications due to bacterial invasion and extra intestinal complications due to immune mediation involving two organ systems, warranting simultaneous treatment with antibiotics and intravenous immunoglobulins.*

Keywords: *Typhoid fever, Complications, Children.*

The whole course of the illness of this 17 years old child spanned over 30 days. This patient had one week fever and malena, which was treated with cefixime without any laboratory investigations in her native village. With oral cefixime, fever subsided after 7 days. This was the course in the first week of illness. After 2 weeks of afebrile period, i.e on the 3rd week of illness, child presented to Apollo children hospital, Chennai with recurrence of fever, unsteadiness and gastrointestinal bleeding.

On arrival in the hospital at 3rd week of illness child was febrile, anemic and vital signs were stable. CNS examination showed GCS 15/15, slurred speech, no nystagmus, cranial nerves normal, intention tremors both hands were present. Muscle bulk, tone, power, reflexes and sensations were normal. No signs of meningeal irritation seen. Examination of other systems were normal.

Investigations were done focusing on a recurring febrile illness, lasting for a month, presenting with fever and gastrointestinal bleeding in the first week partially treated with cefixime, presenting with fever, ataxia and pallor in the third week of illness. Positive lab investigations were low Hb 6.6 gm, with WBC and platelet counts in the lower limit of normal. There was raised reticulocyte count (4%), high LDH (1482 U/L), high serum ferritin (17696 ng/mL) and positive Coomb's test. Serum triglycerides elevated (457 mg/dL), serum fibrinogen decreased (900 ng/mL). Bone marrow examination was not done. These laboratory features strongly favored the diagnosis of immune hemolytic anemia and hemophagocytic lymphohistiocytosis (HLH). Investigations for ataxia did not reveal anything positive, Magnetic resonance imaging (MRI) of brain and spine, CSF analysis were all within normal limits. Antibodies such as anti - NMDAR, anti MOGG Antibody and aquaporin 4 Antibody (Anti-AQP4) were all negative. Vasculitis profile was negative. Isolation of Salmonella typhi in the blood culture and high CRP (69.1) was the connecting link between all the issues in the child. Initially fever with gastrointestinal bleeding responding to cefixime and reappearing again within 3 weeks with ataxia and immune hemolytic anemia all could be explained by a single diagnosis of complicated typhoid.

With the above mentioned clinical and laboratory data, she was diagnosed to have typhoid fever/ acute immune hemolytic anemia/ acute encephalopathy due to isolated demyelination. In view of active salmonella bacteremia, treated with ceftriaxone and azithromycin. It was decided to tackle immune hemolytic anemia and cerebellar ataxia with intravenous immunoglobulin (IVIG) rather than steroids and packed RBC transfusion. She gradually recovered and was discharged. On follow up her hematological and neurological illnesses got resolved completely. The final diagnosis was complicated typhoid fever with immune hemolytic anemia and acute cerebellar ataxia.

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Discussion

The febrile episode which occurred 3 weeks prior to admission could have been an undiagnosed typhoid fever. The treatment at native place with tab cefixime caused defervescence but recurred because of inadequate duration of treatment. In this child the intestinal complications were limited to abdominal pain, hematochezia and malena. These could be due to typhoid ulcers caused by bacterial invasion of mucosal and sub mucosal layers of small bowel. In bacteremic phase of salmonella infection the child developed extra intestinal complications. DCT positive hemolytic anemia has occurred as an immune mediated complication in this child. Anemia due to hemophagocytosis has already been reported in literature as a hematological complication of typhoid fever. Acute cerebellar ataxia also has been reported as neurological complication of typhoid fever. Uniquely two extraintestinal complications-hematological and neurological - occurred in this child. Adequate treatment with antibiotics and IVIG seems to have tackled both para and post infectious sequelae of typhoid fever, thereby facilitating complete recovery.

The lesson what we learned from this child and want to share is to elicit a complete history spanning over a month and considering this as the manifestation of a single diagnosis, rather than a disease with multiple problems though unconnected. Complete recovery of the child from all these issues is the final proof for our approach. This case is complex as she developed both intestinal and extraintestinal complications almost simultaneously. The intestinal complications are infection related while extra intestinal complications are immune mediated. The occurrence of complications involving 2 extra intestinal systems in the same patient at the same time is unusual. Hence we reported this rare case to serve as a reminder that enteric fever has to be treated for an adequate duration and vulnerability for complications does exist.

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CLIPPINGS

Successful Management of Complex Pediatric and Neonatal Wounds With Methylene Blue and Gentian Violet Foam Dressings

Methylene blue and gentian violet (MB/GV) foam dressings can keep wound beds moist, decrease ongoing inflammation, provide antibacterial coverage and promote healthy wound edges.

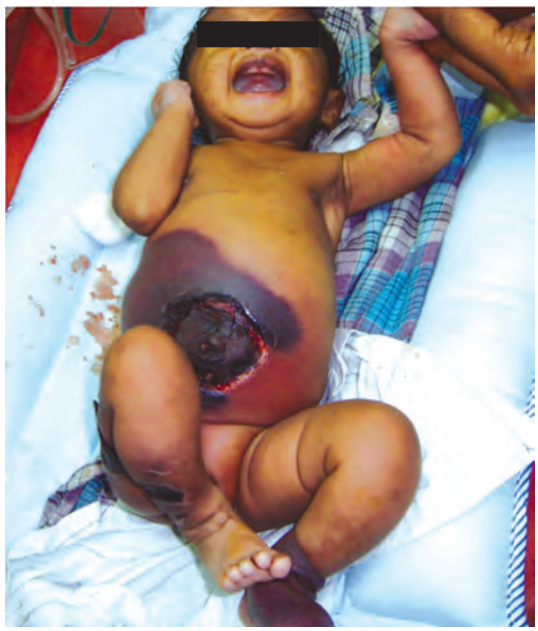
Eight patients (6 infants and 2 adolescents) included infants with giant omphalocele epidermal stripping, dehisced abdominal wounds, peristomal dermatitis and peripheral intravenous extravasations and adolescents with stage 4 pressure injuries were included. The treatment goals were to optimize the wound bed through debridement, elimination of bioburden, providing moisture balance and enhancement of granulation tissue growth. They received MB/GV foam dressings every 2 to 3 days along with standard of care (SOC) management.

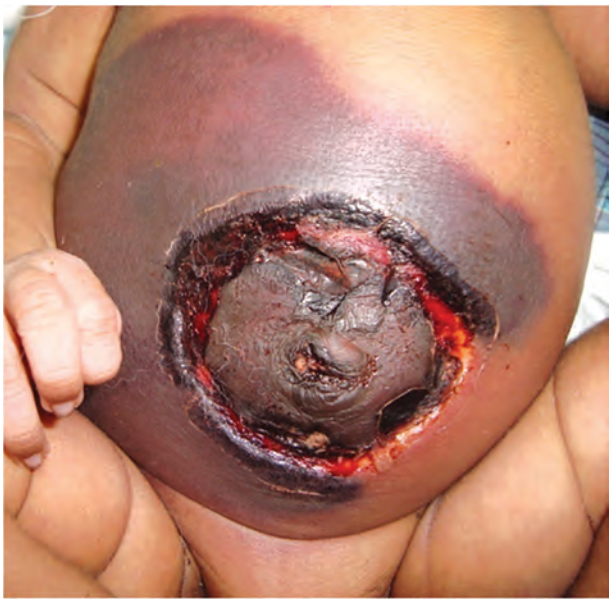
Effective debridement, bioburden elimination, moisture balance and edge enhancement were achieved in all wounds. Three cases were considered for negative pressure wound therapy (NPWT), but was not used because of challenging clinical characteristics and wound locations. Instead, MB/GV polyvinyl alcohol foam provided capillary wicking action that enhanced wound closure without NPWT. No side effects were observed.

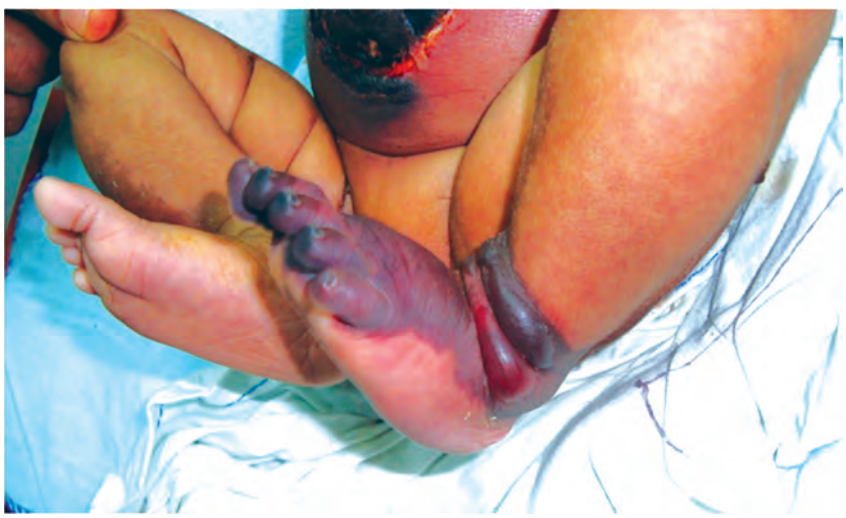
Methylene blue and gentian violet foam dressings appear to be a safe clinical option for antibacterial coverage, moisture management and debridement in neonatal and pediatric patients.

Vita Boyar. Successful Management of Complex Pediatric and Neonatal Wounds With Methylene Blue and Gentian Violet Foam Dressings Wounds 2021; 33(10):253-259.

PICTURE QUIZ







An infant was referred from a peripheral hospital with lesions as shown in the pictures. The child was born at term via naturalis. To begin with, there was a small blackish patch which became confluent over the abdomen followed by similar lesions over the left foot and right leg.

1) Identify the lesions.

Necrotic skin lesions 'Purpura Fulminans'

2) What are the predisposing causes?

Sepsis with DIVC, Vasculitis with thromboembolic manifestations, Protein C deficiency

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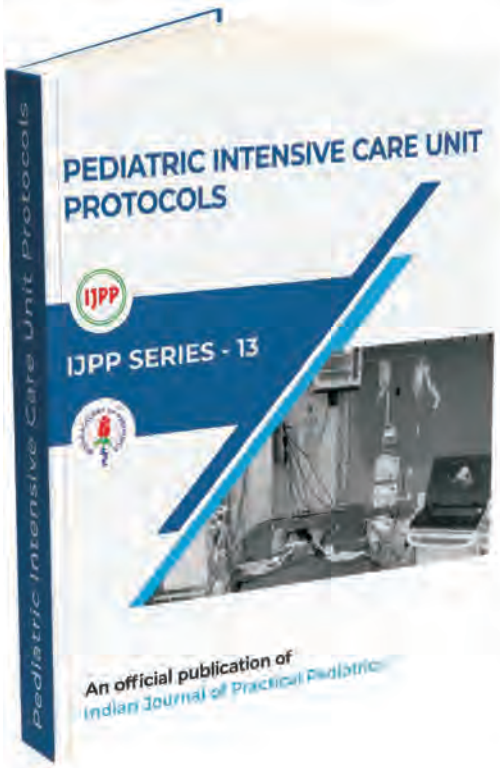

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