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Dr. K.Nedunchelian Editor-in-Chief	**Dr. S. Thangavelu** Executive Editor

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Pedicon 2011 Jaipur

Earnest Endeavours - Expanding Horizons.....

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RHEUMATOLOGY

JUVENILE IDIOPATHIC ARTHRITIS

** Panchapakesa Rajendran C*

Abstract: *Juvenile idiopathic arthritis is the commonest pediatric onset rheumatologic disease. JIA represents a heterogeneous group of arthritides of unknown cause, which begin before 16 years of age. The JIA classification identifies seven disease categories, which differ in their clinical presentation, outcome and in some, genetic background also. Although none of the available drugs has a curative potential, the recent advancement in non biological and biological disease modifying anti-rheumatic drugs , have improved the outcome of JIA. In this review classification, clinical features and recent advances in the management of JIA have been discussed.*

Keywords: *Juvenile idiopathic arthritis, classification, disease modifying anti-rheumatic drugs, biological agents.*

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. Many children with JIA have active disease that can persist into adulthood and may result in short or long term morbidity.[1,2] Since JIA can mimic other causes of arthritis in children, the treating physician should be cautious in the diagnosis of this condition, otherwise it can lead on to misdiagnosis.

Juvenile idiopathic arthritis (JIA) is a group of diseases characterized by chronic synovitis with number of extra articular manifestations. JIA is defined as arthritis involving atleast one joint, that begin before the age of sixteen years, persists for more than six weeks and other known causes have been excluded.

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Chennai.

Classification

The different classification criteria are juvenile rheumatoid arthritis(JRA) proposed by American College of Rheumatology(ACR),[3] juvenile chronic arthritis(JCA) developed by European League Against Rheumatism (EULAR)[4] and the new term juvenile idiopathic arthritis (JIA) by International League of Association of Rheumatologists (ILAR) (Table 1). The JIA classification criteria was described first time in 1995,[5,6,7] later revised at Durban in 1997 [6] and again in 2007 at Edmonton.[7] The details of ILAR classification is given in (Table 2).

Epidemiology

The incidence and prevalence vary among ethnic and geographically different population. The overall prevalence of JIA is estimated to be from 0.07 to 4.1 per 1000 children, with an incidence of 0.008 to 0.226 cases of JIA per 1000 children.[8] While oligoarticular being 40% of newly diagnosed among Caucasian population, polyarticular is predominant in African, East Indian and Indian population. In a study of 495 JIA cases from Chennai, South India systemic onset was 105 (21.2%) oligo arthritis 75 (15.2%), polyarthritis 175 (35.3%), enthesitis related arthritis 131(26.46%), psoriatic arthritis 8 (1.6%) and undifferentiated arthritis 1 (0.2%).[9]

Table 1. Different classifications of childhood arthritis

ACR Juvenile rheumatoid arthritis JRA	EULAR Juvenile chronic arthritis JCA	ILAR Juvenile idiopathic arthritis JIA
Duration of disease 6 weeks or longer	Duration of disease 3 months or longer	Duration of disease 6 weeks or longer
Systemic- characteristic fever with arthritis	Systemic- characteristic fever with arthritis	Systemic
Polyarthritis- 5 and above joints	Polyarticular-5 and above joints- RF negative	Polyarthritis -RF-Negative
	Juvenile rheumatoid arthritis- 5 and above joints-RF positive	Polyarthritis- RF-Positive
Oligoarthritis-4 and less joints	Pauciarticular-4 and less joints	Oligoarthritis Persistent Extended
	Juvenile psoriatic arthritis	Psoriatic arthritis
	Juvenile ankylosing spondylitis	Enthesitis related arthritis Undifferentiated arthritis

As per the studies done in North India by Malaviya et al[10] and Aggarwal et al[11] polyarticular JIA was found to be the commonest.

Pathogenesis[8]

The pathogenesis of JIA is not fully understood. There are evidences to show that JIA is an autoimmune disease. The Human Leukocyte Antigen (HLA) class- I, HLA- B27 is associated with enthesitis related arthritis and HLA class-II, DR1 and DR4 are seen in polyarticular RF positive type.

Abnormal autoimmune activity is present in JIA. Tumor Necrosis Factor alpha (TNF alpha) plays a significant role in polyarticular type and interleukin-6 (IL-6) level is increased in systemic type. There are studies to support that JIA is an antigen driven T cell mediated disease. Theories show that immune complex activate inflammatory cascade in JIA. The immuno-pathogenesis of JIA is complex and multifactorial involving T and B cells.

Clinical features[12-15]

JIA is classified into eight categories based on clinical and investigational evidence in the first six months of the disease. These types differ in their clinical presentation, outcome and immunogenetic background, supporting the concept that JIA is a heterogeneous group of arthritides with different pathogenic mechanisms.

Systemic onset JIA (SoJIA)

This type of onset is also known as Still's disease, who made earliest formal description of Juvenile Arthritis in 1897. SoJIA constitute 10-20% of all JIA but highest morbidity occurs in this type. There is equal sex incidence and can occur at any age during childhood.

Table 2. ILAR- Classification criteria of JIA— Edmonton second revision

Categories	Definitions	Exclusions
Systemic onset	Arthritis in one or more joints with or preceded by fever of at least two weeks duration that is documented to be daily (‘quotidian’) [a] for at least 3 days and accompanied by one or more of the following: 1) Evanescent (non fixed) erythematous rash 2) Generalised lymph node enlargement 3) Hepatomegaly and/or splenomegaly4) Serositis [b]	A,B,C,D
Oligoarthritis	Arthritis affecting 1 to 4 joints during the first 6 months of disease. Two subcategories are recognized: 1. Persistent oligoarthritis: affecting not more than 4 joints throughout the disease course. 2. Extended oligoarthritis affecting a total of more than 4 joints after the first 6 months of disease.	A,B,C,D,E
Polyarthritis (RF Negative)	Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative	A,B,C,D,E
Polyarthritis (RF Positive)	Arthritis affecting 5 or more joints, during the first 6 months of disease; two or more tests for RF at least three months apart, during the first 6 months of disease is positive.	A,B,C,E
Psoriatic arthritis (PsA)	Arthritis and psoriasis or arthritis and at least two of the following 1) Dactylitis [c] 2) Nail pitting or onycholysis 3) Psoriasis in a first degree relative	B,C,D,E
Enthesitis related arthritis (ERA)	Arthritis and enthesitis,[d] or arthritis or enthesitis with at least 2 of the following 1) Presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain [e] 2) Presence of HLA-B27 antigen. 3) Onset of arthritis in a male over 6 years of age. 4) Acute (symptomatic) anterior uveitis 5) History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter’s syndrome or acute anterior uveitis in a first degree relative.	A,D,E
Undifferentiated arthritis	Arthritis that fulfils criteria in no category or in two or more of the above categories	

Contd...

Exclusions

A. Psoriasis or history of psoriasis in the patient or first degree relative.

B. Arthritis in a HLA-B27 positive male beginning after the sixth birthday.

C. Ankylosing spondylitis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, Acute anterior uveitis or a history of one of these disorders in a first degree relative.

D. Presence of IgM rheumatoid factor on two occasions at least three months apart.

E. Presence of systemic JIA in the patient.

Details

a. Quotidian fever is defined as a fever that rises to 39^0 C once a day and returns to 37^0 C between fever peaks.

b. Serositis denotes pericarditis or pleuritis or peritonitis.

c. Dactylitis is swelling of digits ,which extends beyond the joint margin.

d. Enthesitis is defined as inflammation at the site of insertion of a tendon, ligament, joint capsule or fascia to bone.

e. Inflammatory lumbosacral pain refers to lumbosacral pain at rest and morning stiffness that improves on movement.

The characteristic of fever will be one or two spikes a day in the evening or early morning lasting for few hours, comes back to normal and subside on its own, whether treatment is given or not. During the peak of the fever evanescing maculo papular rash occurs predominantly in the covered portion of the body. The other manifestations are lymphadenopathy, hepato-splenomegaly, pericarditis and rarely myocarditis.

The clinical course is variable. Systemic features like fever may precede arthritis by weeks or months. In 50% of cases the extra articular features subside during initial years of the disease. The polyarticular course of the disease involving larger and smaller joints will be progressive in nature. Many patients who have persistent active disease, develop cervical spine involvement that will lead on to ankylosis.

Because of the prolonged disease activity, physical inactivity and glucocorticoid treatment severe osteoporosis can occur that can lead on to fracture .To prevent this complication adequate prophylaxis and treatment with calcium, vitamin D and also bisphosphonates is required. Due to the same reasons growth abnormalities can occur. Rarely secondary amyloidosis may occur due to persistent disease activity for many years.

Macrophage activation syndrome (haemophagocytosis) is a rare, life threatening complication of SoJIA. There will be aggressive proliferation of macrophages and histiocytes which phagocytose other blood cells. The irregular fever in SoJIA will become continuous along with hepatosplenomegaly, lymphadenopathy, coagulopathy with hemorrhagic manifestations and neurologic symptoms. The laboratory abnormalities include abnormal liver function, pancytopenia, hypofibrinogenemia, normal ESR, increased triglycerides and ferritin level. Haemophago-cytosis by macrophages will be seen in bone marrow aspiration study. The treatment includes steroids and cyclosporine.

Oligoarthritis JIA

In this type, girls are more commonly affected and usually occurs under the age of 6 years. It involves mainly knees, ankles and joints will be swollen but pain may not be severe. A limp may be the only sign of the disease. ANA positivity can occur in this type with the risk of developing asymptomatic chronic anterior uveitis (inflammation of iris and ciliary body).If early diagnosis has not been made it can lead on to complications including cataract, glaucoma, posterior synechiae, band keratopathy and loss of vision and so it requires glucocorticoid and mydriatics eye drops, systemic steroids or subtenon injection, (injection through tenon the thin membrane which envelops the eyeball from optic nerve to limbus) immunosuppressives and sometimes biological agents.

The subtype extended oligo arthritis will behave like polyarthritis type and can lead on to erosions and deformities.

Polyarthritis JIA

Rheumatoid factor positive type usually affects girls in late childhood. Because of the development of severe arthritis with bony erosion and extraarticular manifestation including rheumatoid nodules, it is called adult type of JIA. The manifestations will be symmetrical polyarthritis involving larger and smaller joints including metacarpophalangeal, interphalangeal, temporomandibular joints and cervical spine.

Rheumatoid factor negative type occurs throughout childhood and the disease severity will be less. ANA positivity can be associated with chronic anterior uveitis.

Enthesitis related arthritis

This type is characterised by enthesitis at the site of insertion of tendo achilles, plantar fascia and also in tarsal area. Asymmetrical arthritis predominantly affecting the lower limbs will occur. Hip joint involvement is not uncommon and erosion at the site of enthesitis can be found. Eye involvement as symptomatic recurrent acute anterior uveitis is a frequent extra articular manifestation. Boys above the age of 6 years are affected and are often HLA B27 positive. Many children in this type may develop sacroiliac and spinal joint involvement. Ultimately some develop one of the spondyloarthropathies like Juvenile onset ankylosing spondylitis and undifferentiated spondyloarthropathy.

Psoriatic arthritis (PsA)

PsA is rare in children. Arthritis can precede skin lesions by many years. Apart from oligoarticular and polyarticular manifestations , axial joint involvement can occur. The arthritis can be chronic and destructive, requiring immunosuppressive treatment used for children who have polyarthritis JIA.

Differential diagnosis

A detailed history and clinical examination with laboratory support will be useful, not only in making the diagnosis of JIA but also to find out the type of onset.The differential diagnosis is given in (Table-3).

Since 15% of leukemic (usually acute lymphoblastic leukemia) patients can present initially with musculoskeletal manifestations, it has become an important differential diagnosis for SoJIA and the features are as follows.1) Fever may not be quotidian but can be continuous 2) Pain in the joint is not proportionate to the degree of involvement 3) Night pain and bone pain can be predominant 4)Anemia will be disproportionate to the duration of the disease 5) Elevated lactate dehydrogenase level 6) Leucopenia and thrombocytopenia in contrast to polymorpho leucocytosis and thrombocytosis in SoJIA.

Table 3. Differential diagnosis

Systemic onset JIA	Oligoarthritis JIA	Polyarthritis JIA
Rheumatic fever	Septic arthritis	Systemic Lupus erythematosus
Leukemia	Reactive arthritis	Dermatomyositis
Systemic Lupus Erythematosus	Hemophilia	Spondyloarthropathies
Juvenile dermatomyositis	Tuberculosis	Serum sickness
Vasculitis	Villonodular	Leukemia
Infective endocarditis	synovitis	Immune deficient states

Investigations

Laboratory tests should not be solely relied upon to make the diagnosis of JIA. Children with JIA usually have normochromic normocytic anemia, polymorphonuclear leucocytosis, thrombocytosis and elevation of erythrocyte sedimentation rate and C-reactive protein. RF will be positive in less number of patients with JIA(polyarticular RF positive). Anti-Cyclic citrulinated peptide (Anti.CCP) is positive mostly in patients with RF positivity. ANA can be positive mostly in oligoarticular type and less frequently in polyarticular type. HLA-B27 can be positive in Enthesitis Related Arthritis (ERA). False positive Anti Streptolysin-O, can occur due to inflammation and polyclonal B cell activation–anamnestic reaction.

X-rays show soft tissue swelling, subchondral osteoporosis, periosteal elevation and rarely bony erosion. Cervical spine x-ray is useful in diagnosing fusion and atlanto axial subluxation. Ultrasound with high power Doppler and Magnetic resonance imaging are useful in the early detection of synovitis and erosion.

Treatment

Being a chronic disease that can cause significant morbidity, JIA requires an early and aggressive treatment. For good results a multidisciplinary approach is necessary with Rheumatologist, physiotherapist, occupational therapist, orthopedic surgeon, pediatrician, psychologist and social worker.

Non steroidal anti inflammatory drugs (NSAIDs)

NSAIDs are the first line of treatment for symptomatic relief from joint symptoms and fever but it will not change the course of the disease. Commonly used NSAIDs are given in Table 4.[16]

To decide about the efficacy of particular NSAID, it should have been tried at least for two weeks. The side effects are many which includes gastritis, gastric ulcer, liver enzyme elevation and central nervous system symptoms like head ache, mood changes and tinnitus. Pseudoporphyria is a rare side effect of commonly used napoxen characterized by a blister formation, healing with hypopigmentation in sun exposed areas in fair skinned children.

Glucocorticoids

Glucocorticoids play an important role in the management of JIA. Oral prednisolone (0.5 to 1mg /kg/day in tapering dose)is used in systemic type as a bridge therapy. ie till disease modifiying anti rheumatic drugs (DMARDs) start

Table 4. NSAIDs for JIA

Drug	Dose	
Ibuprofen	35-40 mg/kg/day	tid
Naproxen	15-20 mg/kg/day	bid
Indomethacin	1-3 mg/kg/day	tid
Diclofenac	2-3 mg/kg/day	tid
Meloxicam	0.25 mg/kg/day	od
Celecoxib	6-12 mgkg/day	bid
Etodolac (after 6 years)	20 mg/kg/day	od

acting. A course of low dose prednisolone could be considered for reduction of pain and stiffness in children with severe polyarthritis. The severe manifestations like pericarditis and myocarditis require intravenous pulse therapy with methylprednisolone (30mg/kg/day for three days). Intra articular (IA) steroid injections with Triamcilone Hexacetonide (0.5-1mg/kg/joint) are frequently needed especially in oligoarticular type. Gadolinium contrast-enhanced MRI performed before, at 7 weeks and at 13 months after 1mg/kg IA injection, demonstrated marked improvement in synovitis, with no structural damage.[17] Moreover, children with pauciarticular JRA who received IA steroids within first 2 months of diagnosis demonstrated no leg-length discrepancies as compared to a group of children who had been treated primarily with NSAIDs for several years.[18] Apart from the known common side effects of the steroids, growth arrest or retardation should not be forgotten.

Disease modifying anti -rheumatic drugs (DMARDs) Methotrexate is the commonly used first line DMARD in JIA. This can be given orally, subcutaneously or intramuscularly. This drug starts acting after eight to twelve weeks. It is safe, effective and well tolerated in patients with JIA. Folic acid is administered to reduce the frequency and severity of side effects. Liver function tests and blood counts should be done every three months to monitor the side effects. Tapering the dose of methotrexate can be attempted twelve months after complete remission.

Sufasalazine is primarily used in ERA and also in combination with methotrexate in polyarthritis. It is better to avoid in SoJIA when systemic manifestations are present. Blood counts and liver function tests should be done periodically.Hydroxychloroquine(HCQ) is usually given in combination with methotrexate but ophthalmic examination should be done every six months. Leflunomide, Cyclosporin and Thalidomide are rarely used. The doses and side effects of DMARDs are given in Table 5.

Biological agents

These drugs are usually used when non-biological DMARDs do not give good results. Tumor necrosis factor alpha inhibitors are commonly used biological agents. Screening for tuberculosis with mantoux and x-ray chest should be done before the initiation of therapy with biologial agents and steroids, as it can cause reactivation of the disease. Patients should be monitored for other infections also.

Table 5. DMARDs for JIA

Drug	Dose	Side effects
Methotrexate	0.5to1mg/kg/once a week	Mucosal ulceration, nausea Vomiting, loss of appetite Hepato toxicity, bone marrow toxicity
Sulfasalazine	12.5 to 50 mg/kg/day bid	Rash, gastrointestinal toxicity, Bone marrow toxicity
Hydroxychloroquine	6mg/kg/day	Nausea, vomiting, ocular toxicity
Cyclosporin	3to5 mg/day bid	Hypertension, renal toxicity, Hypertrichosis
Leflunomide	3 to 10 mg/day	Teratogenicity, hepatotoxicity, Mucosal ulceration, diarrhoea

Etarnercept is the more commonly used TNF alpha inhibitor in JIA. It is a chimeric molecule of a soluble TNF receptor coupled to the Fc fragment of IgG1. This binds to the circulating TNF alpha, which is a major cytokine in causing inflammatory synovitis and reduce the quantity of TNF alpha. The dose of etarnercept is 0.4mg/kg (maximum 25mg), to be given as subcutaneous injection two times a week. The common side effects are local injection site reaction, fever and rash.

Infliximab is a chimeric human /mouse IgG1 anti TNF alpha antibody. It binds both soluble and membrane bound TNF alpha. It is administered by intravenous infusion 0, 2, 6 and thereafter every 8 weeks. The dose is 3 to 5mg per kg. Adalimumab is a recombinant fully humanized monoclonal antibody that binds to TNF alpha. It is administered by subcutaneous injection on a weekly to alternate week schedule.

Anakinra[19] is a recombinant IL-1 receptor antagonist and it is given daily by subcutaneous injection in a dose of 0.1mg/kg/day. In SoJIA administration of anakinra was associated with marked improvement.

Tocilizumab (TCZ)[20] is a humanized monoclonal IL-6 receptor antibody which is a useful drug in SoJIA given at a dose of 8mg/kg every 2 weeks for 3 months. The side effects were infections and mild liver enzyme elevation.

Abatacept[21] is a fusion protein linking the extacellular domain of human cytotoxic T-lymphocyte associated antigen-4(CTLA-4) to the FC portion of humanIgG1.It acts by competing for the binding of CD28 on T cell and CD80/86 on the antigen presenting cell. This costimulatory signal ,which is necessary for T cell activation is blocked. This is the recently approved biological agent for JIA. Abatacept has been studied in children with polyarticular JIA, including those who have failed other biological therapies, showed good improvement.Rituximab is an anti CD20 monoclonal antibody that causes B cell depletion.

Other therapy

Autologous stem cell transplantation has been tried in SoJIA who have been resistant to treatment. This procedure is associated with significant morbidity and mortality.

Physical therapy

Physiotherapy and occupational therapy are important components in the management of JIA. They are helpful to maintain the strength of the muscles and the mobility of the joints. Depending upon the joints involved, severity of arthritis and degree of deformity, mobilization and strengthening exercises should be given. And different kinds of splints may be used for the prevention and correction of deformities. Swimming and cycling which do not put weight on joints should be encouraged.

Psychosocial development

Psychological assessment can be done periodically by counseller or psychologist. The children with JIA should be encouraged to attend school regularly and participate in recreational activities in whatever possible way.

Surgery

Surgery should be considered in children with JIA whose joint cartilage is destroyed. Total joint replacements are being performed with great success for young people who have JIA. The longevity of the replaced joint must be considered when planning on such surgery.

Outcome[22]

Severe arthritis at the onset of the disease, persistently active disease, early development of bony erosion, early involvement of hip joints are markers for poor prognosis. Even though there is no cure in spite of advances in therapy like methotrexate and biological agents, long remission of the disease activity can be achieved. Most of the time the prognosis of polyarticular and systemic onset types is unpredictable. Bony erosion and deformities can occur in polyarticular rheumatoid factor positive type. Since asymptomatic uveitis in olygoarticular type can produce long term morbidity, it should not be missed.

Points to Remember

- ***Juvenile idiopathic arthritis is not an uncommon rheumatic disease in children and it can mimic many other diseases.***
- ***Since prognosis and treatment vary with the type of onset, it should be established.***
- ***Treatment with immunomodulatory therapies are becoming more common in this pediatric population.***
- ***Early detection and aggressive treatment is required for the complications of JIA.***

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NEWS AND NOTES

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RHEUMATOLOGY

SYSTEMIC ONSET JUVENILE IDIOPATHIC ARTHRITIS – REVIEW OF CLINICAL FEATURES AND MANAGEMENT

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Abstract: *Systemic juvenile idiopathic arthritis (sJIA) is one of the autoinflammatory disorders of childhood. It is characterised by systemic features such as fever, rash and organ involvement, in addition to arthritis. Diagnosis is mainly clinical and one of exclusion. Management is directed towards supportive management, treatment of systemic features and articular manifestations. Drugs for treatment of systemic features include NSAIDs, steroids and cyclosporine. Treatment of arthritis is with intra-articular steroid injections and methotrexate. Biological therapies such as anti-TNF agents, anti IL-1 inhibitor and anti IL-6 inhibitor are being increasingly used in the management of refractory disease. The course of the disease can be fluctuant with flares and remissions. Major causes of death are Macrophage Activation Syndrome (MAS), amyloidosis with renal failure and secondary infections. About half of the children progress despite treatment and have functional disabilities.*

Keywords: *Systemic JIA, Systemic arthritis, Management, Biologic agents.*

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Systemic onset Juvenile Idiopathic Arthritis (sJIA) is an auto-inflammatory disease of childhood and is classified as one of the subtypes of Juvenile Idiopathic Arthritis (JIA).

History

The earliest depiction of sJIA is a painting by Caravaggio in the 17th century showing a young boy with joint deformities, muscle atrophy, jaundice and abdominal distension. The first scientific description of this disease was by Sir George Frederick Still, who in 1897 highlighted its unique features, accounting for the disease being referred to, by some as 'Still's disease'.[1]

Epidemiology

Systemic arthritis constitutes 10-20% of all JIA, but accounts for two-thirds of the mortality.[2] The incidence is probably around 0.4–0.8 per 100000. Males and females are almost equally affected (in variance with the usual female predominance in other subtypes of JIA), with a slight preponderance of females if the onset of disease is after 10 years of age. It can occur at any age from infancy to adolescence, but in two-thirds of patients the onset is under 5 years of age. Proposals of a viral etiology or seasonal variation have not been substantiated.

Genetics and pathogenesis

Systemic JIA is rarely familial. Polymorphisms of cytokine genes may determine predisposition to systemic arthritis. The presence of HLA class DR5, DR8, Dw7 and possibly DR4, has been reported to be associated with sJIA, although not consistently so.

The most important pro-inflammatory cytokines involved in the pathogenesis of systemic JIA are Interleukin-6 (IL-6), Interleukin-1 (IL-1) and tumour necrosis factor-α (TNF- α). De Benedetti and Martini suggested that systemic JIA is an IL-6 mediated disease.[3] IL-6 has been found to be markedly elevated in blood and synovial fluid and levels have been shown to increase just prior to febrile spikes. In addition, abnormalities in IL-6 regulation may account for the growth abnormalities, thrombocytosis and microcytic anaemia, associated with sJIA. Auto-antibodies and immune complexes do not play a major role in pathogenesis.

Clinical features

Systemic JIA is characterised by the systemic toxicity and extra-articular manifestations that occur during a disease flare. The ILAR (International League of Associations for Rheumatology) criteria for diagnosis of Systemic JIA are given in Table 1.[4]

Fever is essential to make a diagnosis. The typical fever pattern is a quotidian type, with rapid spikes of temperature to more than 39°C, usually in the late afternoon or evening, followed by rapid resolution to or below baseline. Chills can occur, but rigor is rare. Although unusual, fever can sometimes manifest after the onset of arthritis.

The febrile spikes are often accompanied by a classic rash, which is a salmon-pink coloured rash, most prominent over the chest, abdomen, back and inter-triginous areas. It is usually macular, lesions being 3 to 5 mm in diameter, often with central clearing, although they can be urticarial. It is pruritic in 10% of patients, with a resultant Koebner phenomenon. The rash can be difficult to identify in dark skinned individuals.

Reticulo-endothelial involvement is common, characterised by hepatomegaly, splenomegaly and generalised lymphadenopathy. Mild elevations of serum transaminases occur

Table 1. ILAR classification criteria for sJIA

Arthritis in any number of joints together with a fever of at least 2 weeks duration that is documented to be daily (quotidian) for at least 3 days and is accompanied by one or more of the following:

- Evanescent rash
- Generalised lymphadenopathy
- Enlargement of liver or spleen
- Serositis

Exclusions

- Psoriasis or a history of psoriasis in the patient or a first-degree relative
- Arthritis in an HLA B27 positive male beginning after the sixth birthday
- Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis or a history of one of these disorders in a first-degree relative
- The presence of IgM RF on at least two occasions at least 3 months apart

frequently, Aspartate aminotransferase (AST) being more frequently elevated than Alanine aminotransferase (ALT). It is sometimes difficult to determine whether this reflects disease activity or the use of potentially hepatotoxic medication. Liver histology shows non-specific periportal inflammatory cell infiltration and Kupffer cell hyperplasia. Chronic liver disease does not occur in childhood systemic arthritis. Rarely, severe hepatic dysfunction or fulminant hepatic failure may occur. Lymphadenopathy is usually symmetric and can be quite prominent. Mesenteric lymphadenopathy can occur leading to abdominal pain or distension. Splenomegaly is most prominent within the first years after onset, but Felty's syndrome or functional hyposplenia are not associated.

Serosal inflammation is a characteristic feature of Systemic JIA. Pericarditis is the most common, followed by pleuritis and peritonitis. Pericarditis occurs in 3 to 9% of patients, is often asymptomatic and diagnosed by echocardiography. Rarely, cardiac tamponade or constrictive pericarditis may occur. Myocarditis is much less common and may result in cardiomegaly and congestive heart failure. Endocarditis and valvular involvement are exceedingly rare. Parenchymal pulmonary disease is rare, but interstitial fibrosis has been described. Pleural effusions may occur with carditis or may be incidentally seen on chest radiographs. Sterile peritonitis is known to occur and can cause severe abdominal pain.

Arthritis may be present at onset or can develop during the disease course. The onset is usually oligoarticular, but the course can be polyarticular. Knees, wrists and ankles are most commonly affected, but hips, cervical spine, tempromandibular joints and small joints of hands are involved in more than half of the patients. Severe polyarthritis can be resistant to treatment and is often destructive, resulting in significant disability. Tenosynovitis occurs in 10% of patients, the most common sites being extensor tendon sheaths of the dorsum of the hand and the foot, the posterior tibial tendon and the peroneus longus and brevis tendons. In contrast to other forms of juvenile arthritis, involvement of eyes is distinctly unusual in Systemic JIA, but asymptomatic uveitis needs to be watched out for.[5]

Complications

Macrophage activation syndrome (MAS) is a complication of sJIA, associated with significant mortality and morbidity. It is a form of secondary hematophagocytic lympho histiocytosis (HLH).[6,7] MAS is characterised by rapid onset of persistent high fever, lymphadenopathy, hepatosplenomegaly, bleeding dyscrasias, hepatic dysfunction and altered sensorium. The laboratory features include anemia, neutropenia, thrombocytopenia and extremely high ferritin levels. Low fibrinogen levels and increased levels of fibrin degradation products reflect disseminated intravascular coagulation (DIC). Prothrombin time and partial thromboplastin time are prolonged and blood levels of Vitamin-K dependent clotting factors are decreased. ESR is paradoxically low due to co-existent hypofibrinogenemia, secondary to consumptive coagulopathy and DIC. Histiocytic consumption of red cells and platelets can be demonstrable in bone marrow or lymph node biopsy. Levels of cytokines such as Interferon-α and TNF-α are increased.

The etiology of MAS has not been elucidated, but it can follow infections, particularly by herpes viruses, including Epstein-Barr virus. Earlier reports of onset of MAS with specific therapeutic agents used for sJIA, are thought to be coincidental rather than causative. The histopathologic picture of Kikuchi's disease has been reported in children with MAS. It has

been suggested that children with systemic JIA showing histologic appearances of Kikuchi's disease, should be monitored closely as they are at a much higher risk of HLH. Treatment of MAS is with steroids (intravenous pulsed methyl prednisolone), cyclosporine and in severe cases, etoposide.[6,7] Early recognition and supportive management are vital in reducing mortality due to MAS.

Secondary amyloidosis can occur due to long-standing inflammation. It is suspected if there is persistent proteinuria and confirmation is by renal or preferably rectal biopsy. Scintigraphy using a radio-iodinated serum amyloid-P component ('SAP scan') is useful as a non-invasive technique for detection and monitoring response to therapy. The aim of treatment is to try and arrest the underlying inflammatory process, although chlorambucil can improve survival.

Growth abnormalities are frequently seen in sJIA due to concurrent hypercatabolism and anorexia. In addition, the frequent requirement of steroids has a detrimental effect on growth. Growth hormone levels are often normal, but levels of Insulin-like growth factor (IGF) are found to be reduced. Systemic arthritis is known to be characterized by markedly elevated circulating levels of IL-6. An IL-6-mediated decrease in IGF-I production has been demonstrated in transgenic mice model and represents a major mechanism by which chronic inflammation affects growth.[3]

Diagnosis and differential diagnosis

The diagnosis of systemic JIA is clinical and is one of exclusion. The diagnosis might be especially difficult, early in the course of disease. Meticulous consideration of features is necessary to distinguish it from other disease entities. It is vital to remember that malignancies including leukaemia can masquerade as systemic arthritis.

Possible differential diagnoses are listed in Table 2.[5] Manifestations that should raise suspicion of another diagnosis are non-articular bone pain and bony tenderness, back pain as a presenting feature, severe constitutional symptoms and the child looking ill even during afebrile episodes, persistent diarrhoea and

Table 2. Differential diagnoses for sJIA

Malignancy
Infection
Bacterial endocarditis
Acute rheumatic fever
Cat scratch disease (Bartonella)
Lyme disease (Borrelia burgdorferi)
Brucellosis
Others
Inflammatory bowel disease
Connective tissue diseases
Systemic lupus erythematosus
Dermatomyositis
Vasculitis
Polyarteritis
Kawasaki disease
Castleman's disease
Familial Mediterranean fever
Episodic fever syndromes
Mevalonate kinase deficiency (hyperimmunoglobulin D syndrome)
Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA)
TNF receptor-associated periodic syndrome (TRAPS)
Muckle-Wells syndrome
Familial cold autoinflammatory syndrome
Chronic infantile neurologic cutaneous and articular syndrome (CINCA)

significant weight loss, hard hepatosplenomegaly/ lymphadenopathy, leucopenia and thrombocytopenia, discordant ESR and elevated LDH (Lactate Dehydrogenase).[8]

Investigations

Laboratory features are supportive rather than being of diagnostic value in systemic arthritis. The characteristic abnormalities are anemia, thrombocytosis and leucocytosis. Leucocyte counts can be higher than $30\text{-}50\times10^9$/L and are predominantly polymorphonuclear cells. Leucopenia or thrombocytopenia can occur rarely. CRP and ESR are elevated, ESR often being more than 100 mm/h and ferritin levels are very high. Polyclonal hypergammaglobulinemia is seen, but rheumatoid factor and antinuclear antibodies are uncommon. Complement levels are usually increased, which helps to distinguish it from SLE. Synovial fluid, if analysed, shows a cell count of 10 to 40,000/ mm^3, predominantly polymorphonuclear leukocytes.[5]

Radiography is not routinely used in clinical practice. However it might be helpful in demonstrating evidence of arthritis in situations of clinical uncertainty. If imaging is performed, radiological abnormalities include soft tissue swelling, osteopenia, periosteal new bone formation, joint space narrowing, growth abnormalities, delayed bone age, erosions, subluxation, ankylosis and joint destruction.

Management

Children with systemic JIA can be acutely ill, often needing hospital admission for stabilisation and initial management. In addition to evaluation and work-up to rule out alternative pathology, careful assessment should be undertaken of respiratory and cardiovascular function. The possibility of MAS should be borne in mind. The general principles of management are directed towards control of extra-articular systemic features and the treatment of arthritis, in addition to supportive management for complications. Other factors such as growth, nutrition and psychosocial impact, need to be continuously addressed.

Treatment of systemic and extra-articular features: It is appropriate to start NSAIDs as initial therapy. Once the diagnosis is securely established, early use of steroids is beneficial. Intravenous methyl prednisolone is given in a dose of 30 mg/kg/day (maximum of 1 gram/ day) for 3 consecutive days and may need to be followed by oral prednisolone in a dose of 1 to 2 mg/ kg/ day (maximum of 60 mg/day). A second-line agent should be considered when there is persistence of disease on steroids or flare of disease with weaning of steroids.

Cyclosporine has been shown to be effective in a prospective trial of 34 children with systemic JIA, in controlling systemic features, resulting in a rise in haemoglobin level, a fall in ESR and decrease in prednisolone requirement. Major limiting factors to continuation of cyclosporine in this study seemed to be drug-toxicity, disease flare and inefficacy.[9] The dose used is generally 4 mg/kg/day. Cyclosporine is however important in treating Macrophage Activation Syndrome (MAS). Although IVIG has been tried, variable or inconclusive results have been demonstrated in several studies. It is probably only of adjunctive value in severe systemic disease. The usual dose is 2 g/kg/day, given monthly for 6 months.

Treatment of arthritis : NSAIDs and intravenous steroids often alleviate arthritis. Specific therapy is with intra-articular steroid injection of triamcinolone hexacetonide. This is done under a general anaesthetic, especially in young children or if multiple joints are injected.

Methotrexate is used as a DMARD (Disease Modifying Anti Rheumatic Drug) and steroid

sparing agent, although response is not as good as it is for other types of arthritis. The dose is 10 – 15 mg/m^2 administered once weekly, the subcutaneous route being preferred to the oral route.

Other drugs such as chlorambucil, azathioprine and cyclophosphamide have been tried with varying success rates.

Biologic agents : Biologic agents are drugs that target specific molecules in the inflammatory cascade, especially of use in those who do not respond to conventional treatment. The universal concern with these agents is that their long-term safety is not yet firmly established.

Anti-TNF agents seem to be a logical therapeutic option, considering that TNF-α is one of the inflammatory mediators of systemic arthritis. Etanercept, a TNF-α receptor fusion protein can be tried, dose being 0.4 mg/ kg (maximum of 25 mg), given subcutaneously twice a week. However, clinical response has not been as encouraging.[10,11] The German registry showed better clinical response to Etanercept in other subtypes of JIA, rather than sJIA. In this group, only 13 % of sJIA patients achieved complete clinical remission.[10] Monoclonal antibodies to TNF-α, such as infliximab and adalimumab, useful in other subtypes of JIA and uveitis, have been found to be of limited efficacy in anecdotal reports.

The most promising results, published to date, appear to be with the IL-1 receptor antagonist, anakinra. It is given as a daily subcutaneous injection 1 mg/kg/day. In preliminary studies, good responses have been shown as to improvement in fever pattern and active arthritis.[12-14] This was accompanied by improvement in hemoglobin, resolution of leucocytosis, thrombocytosis and raised ESR. Other IL-1 inhibitors have been developed, like a long-acting soluble receptor fusion protein and antibodies, but only preliminary data is available presently.

A recombinant human anti-IL-6 receptor monoclonal antibody (MRA), tocilizumab, is undergoing trials and has shown good response in initial studies.[15] A multinational randomised trial is currently ongoing, which will provide more definitive evidence of efficacy.

Autologous stem cell transplantation (ASCT)

Despite established treatment approaches, nearly half of the children with systemic JIA have persistent disease and exacerbations or depend on high-dose steroids. Systemic JIA was the first autoimmune disease in childhood for which an international treatment protocol of autologous stem-cell transplantation (ASCT) was established, for patients refractory to conventional therapy. More than 50% of these patients reached complete remission. However, flares were observed in 28% of patients after ASCT. In addition, ASCT showed a high treatment-related morbidity and mortality in systemic JIA (9%).[16] In patients whose fever cannot be controlled by steroids, ASCT is considered to be contra-indicated due to the risk of MAS. It is currently recommended that ASCT be considered in children who have failed or have toxicity to methotrexate and biological therapies.

Prognosis

The disease course of sJIA can be punctuated by complications, exacerbations and remissions. About half of the children with sJIA recover almost completely. The rest progress and eventually have significant functional disability. Singh-Grewal et al showed that fever and arthritis at 3 months, an elevated ESR and steroid use at 6 months are predictive of a non-monophasic course of the disease. In this study, 51% of patients had a persistent disease course.[17]

With new treatment strategies and early aggressive therapy, mortality rates are less than 1% in Europe and less than 0.5% in North America.[5] The major causes of death are amyloidosis with renal failure, infections due to iatrogenic immunosupression, MAS, cardiac complications and liver failure.

The management of children with severe, complicated sJIA continues to present substantial difficulties to pediatricians.. However, the new biological therapies directed at IL-1 and IL-6 offer some hope in the future, for effective control of refractory disease.

Points to Remember

- ***Systemic JIA is an inflammatory condition characterised by fever, rash, organ involvement and arthritis.***
- ***Complications include amyloidosis, growth failure and life-threatening complications such as Macrophage Activation Syndrome (MAS).***
- ***Diagnosis is mainly clinical after ruling out alternative pathologies, although laboratory and radiological features can be supportive.***
- ***Management involves supportive therapy, treatment of systemic extra-articular features and articular manifestations, with newer biologic agents.***
- ***The course of the disease is characterised by flares and remissions, with approximately half the children having progressive disease despite treatment.***

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WORKSHOP ON CPAP

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The Department of Paediatrics, All India Institute of Medical Sciences, New Delhi in collaboration with the Department of Neonatology, Institute of Child Health & Hospital for children, Egmore, Chennai is organizing a Neonatal Workshop on CPAP on Sunday 22nd August 2010. The workshop will be conducted by Faculty from AIIMS New Delhi, KIMS, Fernandez Hospital and ICH&HC.

The workshop will focus on practical aspects of CPAP in newborn infants. The one day sessions would include participatory learning in mini-workshops, case discussions and demonstrations with special emphasis on group work in tutorials and problem solving.

Those interested may send registration fees Rs.2000 (overseas US$ 60) (by "Demand Draft" or "at par cheques" payable at Chennai only) in favour of "ICH-NB" payable at Chennai by courier. The number of participants is restricted to the first 60. Workbook and resource material will be mailed to Indian Addresses prior to workshop.

Please contact: Dr. G. Durai Arasan Assistant Professor, Department of Neonatology, First Floor Main Building, Institute of child health & Hospital for children, Halls Road, Egmore, Chennai, PIN code: 600008.

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RHEUMATOLOGY

CHILDHOOD SYSTEMIC LUPUS ERYTHEMATOSUS

*** *Nandini Babhulkar***

Abstract: *Systemic lupus erythematosus (SLE) is an episodic, inflammatory, autoimmune disease characterized by the presence of pathogenic autoantibodies. Children and adolescents represent 15% to 20% of all SLE patients. As compared to adults, children tend to have a more severe disease at onset with a higher rate of organ involvement. The clinical picture ranges from very mild arthralgia , skin rash to life threatening renal disease. Rapid diagnosis and appropriate treatment are necessary to prevent major organ damage. Treatment decisions are based on evidence of organ system involved. The spectrum of therapy ranges from non steroidal anti inflammatory drugs (NSAIDS) to cytotoxic agents like cyclophosphamide and mycophenolate mofetil. Recently targeted biological therapies that achieve specific immunosuppression like Rituximab have emerged as promising alternative in refractory cases. Survival in children with SLE has dramatically improved over past decades due to early diagnosis and aggressive immunosuppressive therapy.*

Keywords: *SLE, Antinuclear antibodies, Cyclophosphamide, Nephritis.*

SLE in children and adolescents is a multisystem disease of unknown etiology characterized by recurrent disease flares. The earliest description of the disease dates back to 13th century when Rogerius named it as lupus which is a Latin word for "wolf" as the dermatitis lesions of SLE appeared similar to those of a wolf bite. In 1872, Kaposi proposed that there were two types of lupus erythematosus, the discoid form and a disseminated form. In 1948, Hargraves and colleagues described the lupus erythematosus (LE) cell heralding a new era by indicating autoimmunity to be the probable underlying cause of SLE. In 1957, Friou applied the technique of immunoflorescence to demonstrate the presence of antinuclear antibodies in the blood of patients with SLE. For many decades quinine and then salicylates, in conjunction with quinine, were used in the treatment until the revolutionary discovery of the efficacy of adrenocorticotrophic hormone and cortisone by Hench[1]. Even today, corticosteroids form the primary therapy for almost all patients with SLE.

Epidemiology

The incidence of SLE varies in different ethnic groups as well as between genders. The suggested incidence in pediatric age group is 6-18/100000 in white and 20-30/100000 in black population. SLE has a strong predilection for females, the ratio of girls to boys with lupus varies from 4:1 to 8:1 depending on the age of onset. Approximately 20% of the patients of SLE present in childhood though the onset below age of 8 years is very rare. The peak age of onset of the first symptom is between 15 and 25 years of age.

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Classification

The 1997 Update of the 1982 American College of Rheumatology (ACR) Revised Criteria is used for Classification of Systemic Lupus Erythematosus (Table.1)

The classification criteria are also used for diagnosis of SLE. Presence of four or more of the 11 criteria serially or sequentially point to the diagnosis of SLE and in adults this is found to have a sensitivity and specificity of 96% for diagnosis.

Etiology and pathogenesis

The exact etiology of SLE , except for drug induced lupus, still remains unknown though there is increasing evidence suggesting that multiple factors like genetics, hormones, environmental factors and infections contribute to the immune dysregulation observed in SLE. Genetic studies have identified risk factors like hereditary deficiency of complement components, major histocompatibility complex class II alleles and allelic variants of the Fc portion of IgG genes. The significantly higher prevalence of the disease in females in the period between menarche and menopause suggests the role of sex hormones like oestrogen and prolactin but the exact mechanism remains unclear. Few studies have shown an association between Epstein-Barr virus infection and SLE but no etiological link has been established.

The pathologic manifestations of SLE are as a result of deposition of immune complexes in various tissues leading to inflammation and tissue damage. An increased number of B lymphocytes are found in patients with lupus which are activated to produce high levels of self reactive autoantibodies. CD8 T lymphocytes and natural killer (NK) cells which normally suppress B lymphocytes are found to be reduced. The NK cells appear to have a functional abnormality characterized by killing defect. Other important aspect of the disease is the inability of the reticuloendothelial system to clear the excess immune complexes formed. Deficiency of complement components C4, C2 and C1Q is also seen. Recently an apoptosis related gene Bcl G (L) expression has been found to be increased in T cells of patients with SLE leading to dysregulation of apoptosis resulting in enhanced cell survival of pro-inflammatory cells.[2]

Clinical manifestations

Constitutional symptoms like fever, fatigue, hair loss and weight loss are seen in children. The most common systemic manifestations are arthritis, cutaneous lesions including malar rash, nephritis and central nervous system involvement. Table.2 summarizes the clinical features and their frequencies in children.[3]

Musculoskeletal : Involvement is seen in 60-80% of the patients and is usually in the form of arthralgia, arthritis, tenosynovitis and myositis. There is a mild to moderate joint and deforming arthritis is uncommon. Avascular necrosis (AVN) is seen in approximately 10% of patients and is associated with long term high dose steroid therapy.

Mucocutaneous: Skin involvement is seen in 50-80% of children at the onset and during active disease. The classic butterfly rash seen on malar prominences and nasal bridge is characteristic but not pathognomonic of SLE. It can also be seen in other conditions like Bloom's syndrome, Cockayne's syndrome and Rothmund-Thomson syndrome. Other cutaneous lesions like vasculitis rash, photosensitive rash are seen but discoid lupus is uncommon in children. Mucosal involvement in the form of painless ulcers on the hard palate and nasal septum are seen in a few children. Erythema of the hard palate is more commonly seen.

Table 1. Revised criteria for classification of systemic lupus erythematosus

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	a) Pleuritis—convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR b) Pericarditis— documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal Disorder	a) Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed OR b) Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	a) Seizures—in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance OR b) Psychosis— in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	a) Hemolytic anemia—with reticulocytosis OR b) Leukopenia— < 4,000/mm3 on > 2 occasions OR c) Lymphopenia—< 1,500/ mm3 on > 2 occasions OR d) Thrombocytopenia—<100,000/ mm3 in the absence of offending drugs
10. Immunologic Disorder	a) Anti-DNA: antibody to native DNA in abnormal titer OR b) Anti-Sm: presence of antibody to Sm nuclear antigen OR c) Positive finding of antiphospholipid antibodies OR an abnormal serum level of IgG or IgM anticardiolipin antibodies, a positive test result for lupus anticoagulant using a standard method, OR a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Table 2. Clinical features of SLE at diagnosis in children and adolescents

Clinical features	Frequency Toronto series (%)	Frequency pSLE literature (%)
Constitutional and generalised symptoms		
Fever	55	60-90
Lymphadenopathy	34	13-45
Hepatosplenomegaly	30	16-42
Organ disease		
Arthritis	78	60-88
Any skin rash	79	60-78
Malar rash	36	22-80
Nephritis	51	20-80
Neuropsychiatric disease	25	5-30
Cardiovascular disease	14	5-30
Pulmonary disease	18	18-40
Gastrointestinal disease	19	14-30

Renal: Renal involvement remains the chief cause of morbidity and mortality in children with SLE. 40-50% of the patients will have renal lupus. The initial manifestation of nephritis is microscopic hematuria (79%) followed by proteinuria (55%) and hypertension (40%). Acute renal failure at presentation is rare. Majority of the patients with SLE will manifest features of nephritis within one year of diagnosis of lupus. The WHO classification (Table.3) lists six categories based on biopsy findings of nephritis which have been revised by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) in 2003. (Table.4)[4]

CNS disease: Neurologic manifestations in children involves both central and peripheral nervous system and together are referred to as neuropsychiatric systemic lupus erythematosus (NP-SLE) . After renal disease, CNS involvement is the most common cause of morbidity and mortality in children. Headache, seizures and cognitive dysfunction are the commonest manifestations. Migraine like vascular headache refractory to standard analgesics is frequent. Rarely a severe unremitting headache may result from CNS vasculitis, cerebral vein thrombosis or raised intracranial pressure. Psychosis seen in children with NP-SLE is in the form of visual or tactile hallucinations and is seen in 30-50 % cases. Cognitive dysfunction in the form of poor scholastic performance is seen in 20-50 % children. Seizures usually generalised tonic-clonic in nature can occur at presentation of disease. Cerebrovascular Disease (CVD) occurs in upto 30% of patients and presents as headache, seizures or stroke and has a strong association with antiphospholipid antibodies.[5] Among movement disorders, chorea is the most frequent

Table 3. World Health Organization (WHO) classification of lupus nephritis

Class I	Normal
Class II A	Minimal change
Class II B	Mesangial glomerulonephritis
Class III	Focal And segmental proliferation
Class IV	Diffuse proliferative glomerulonephritis
Class V	Membranous glomerulonephritis
Class Vi	Glomerular sclerosis

Table 4. Abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis (2003)

Class I	Minimal mesangial lupus nephritis
Calss II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis
Class V	Membranous lupus nephritis
Class VI	Advanced sclerosing lupus nephritis

to occur and is also characterized by presence of antiphospholipid antibodies.

Cardiovascular: The most common cardiac manifestation of lupus in children is pericarditis and pericardial effusion. It is symptomatic in 15-25% cases while it can be detected by echocardiography in upto 68% of patients. Valvulitis and the classic Libman-Sacks endocarditis seen in adults is rare in children. With improved long term outcome, premature atherosclerosis and subsequent complications have become a major cause of morbidity and mortality. Accelerated atherosclerosis is due to inflammatory and immune abnormalities intrinsic to SLE, primary dyslipidemias and secondary effect of steroid therapy.

Pulmonary: Pulmonary involvement is seen in 25-75% of cases and ranges from a subclinical form to clinical spectrum of pneumonia, pleuritis, pleural effusion, pulmonary hemorrhage, pulmonary hypertension and pneumothorax.

Gastrointestinal: Gastrointestinal involvement is seen in 20-40% of patients. Abdominal pain is the most frequent symptom and is related to ascitis, peritonitis, pancreatitis or paralytic ileus. Hepatomegaly occurs in 50-60% of patients and is usually mild. Splenomegaly is seen in 20-30% of cases and functional asplenia is common.

Antiphospholipid syndrome (APS): APS is an acquired hypercoagulation state of autoimmune etiology seen in association with SLE. In children it manifests with arterial and venous thrombosis, leg vein thrombosis being the commonest presentation. It is characterized by presence of antibodies to phospholipids such as cardiolipin.

Laboratory investigations

Hematologic abnormalities seen in SLB are summarised in Table.5. Anemia, leucopenia and thrombocytopenia are seen in 50-70% of patients. The Coomb's test is positive in 30 – 40% of patients. Coagulation abnormalities like prolonged activated partial thromboplastin time and prothrombin time are seen in patients who are lupus anticoagulant positive. In addition complement levels, C3 and C4 are found to be low. Acute phase reactants like ESR are raised,

Table 5. Hematologic abnormalities in systemic lupus erythematosus

Abnormality	Frequency (%)
Anemia (hematocrit < 30%)	50
Acute hemolytic anemia	5
Leucopenia	
<4500 WBC/mm^3	40
<2000 WBC/mm^3	10
Thrombocytopenia	
<150,000 platelets/mm^3	30
<100,000 platelets/mm^3	5

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while C-reactive protein will often be normal except in cases of concurrent infection when it will also be raised. Liver and renal function tests, lipid profile and urine analysis are done in initial evaluation.

Antinuclear Antibodies : Antinuclear antibodies (ANA) are found in up to 100% of patients with SLE. Absence of antinuclear antibodies virtually rules out the diagnosis of lupus. Antibodies to double stranded DNA (dsDNA) are highly specific for SLE and are seen in 60-70% of cases. Other autoantibodies associated with the disease are Anti-Ro (SS_A), Anti-La (SS_B), Anti-Sm, Anti-UI RNP and anti-histone antibodies. Anticardiolipin antibody is seen in 37% of the patients with SLE.

Imaging and Pathology: These will be guided by the clinical manifestations and may include chest X Ray, MRI of brain, renal ultrasound, dual energy x-ray absorptiometry (DEXA) for bone density and renal biopsy.

Treatment

Treatment is challenging because of the chronic nature of the disease characterized by remissions and relapses.

General measures include counseling, education and preventive measures such as use of sunscreens and immunizations including pnuemococcal vaccine. Low fat, calcium rich and no added salt diet is advised, as most of the children will receive steroid therapy. Rest is advised only during active disease and school attendance with normal lifestyle is encouraged.

Pharmacologic management is based on clinical evidence of major organ involvement as well as the severity of the disease and hence is individualized. Five groups of drugs are usually used in the management.

Non Steroidal Anti-inflammatory Drugs (NSAIDS): Most common indication is in the treatment of musculoskeletal diseases. Naproxen is the drug of choice in children and is given in the dose of 10-15 mg/kg/day in two divided doses. It is found to be well tolerated in children and reasonably safe for long term use.

Anti-malarials: Hydroxychloroquine is used in the management of cutaneous manifestations of SLE . It is also used as an adjunct to steroid therapy. Recent evidence suggests that it has a steroid sparing effect as well as a probable role in reversing steroid induced changes in lipid profile. It is also shown to be protective against flares. Hence, now it is recommended to use hydroxychloroquine along with steroids from the onset itself.[6] It is given in the doses of 5-6mg/kg/day and children should be carefully monitored for renal and retinal toxicity.

Glucocorticoids: It forms the mainstay of therapy for its anti inflammatory and immunosuppressive effects. Therapy with low

dose prednisolone 0.5 mg/kg/day is given to control fever, arthritis, dermatitis, serositis, hemolytic anemia and thrombocytopenia. High dose therapy, 1-2 mg/kg/day is used in the treatment of severe nephritis, CNS disease and acute hemolytic anemia. Intravenous methylprednisolone pulse therapy in the dose 30mg/kg/day for 3 days is given when a rapid response is desired in life threatening conditions. Steroid therapy should be tapered gradually once the active disease is well controlled and the patient should be maintained on lowest possible dose needed for well-being. Children should be monitored for adverse effects like osteoporosis, hypertension, peptic ulceration, avascular necrosis and accelerated atherosclerosis. Preventive measures should be taken in the form of use of proton pump inhibitors for gastric protection and promoting weight bearing exercises to prevent osteoporosis. Vitamin D and calcium supplementation should be given to patients on long term treatment.

Immunosuppressive agents: They play a very important role in the management of children with major organ involvement. Most commonly used drugs are cyclophosphamide, azathioprine, cyclosporin and recently mycophenolate mofetil.

Cyclophosphamide: It remains the gold standard in treatment of severe organ involvement especially lupus nephritis and CNS lupus. Intravenous pulse cyclophosphamide in combination with oral steroids is a well proved effective regime. Monthly pulses (500-750mg/m^2 body surface area) of cyclophophamide has become the standard treatment for Class IV nephritis and severe NP-SLE refractory to glucocorticoids and azathioprine.[7] Pulses are given monthly initially and later every three months. Children on cyclophosphamide should be monitored for hemopoietic suppression, infections and in the long term for risk of ovarian failure and malignancy.

Azathioprine: It is used as a second line agent along with steroids in the dose of 1-2mg/kg/day orally. It is recommended in children who do not respond to glucocorticoids and hydroxychloroquine or who develop toxicity to these drugs. Patients on azathioprine should be monitored for myelosuppression, renal and hepatic toxicity.

Cyclosporin: CyclosporinA is an effective steroid sparing immunosuppressant with efficacy comparable to that of cyclophosphamide and azathioprine as reported in adults. In children, because of the high risk of cyclosporin induced nephrotoxicity, its use is limited.

Mycophenolate mofetil: This drug has emerged as a promising therapy for both induction and maintenance of remission in patients with lupus nephritis.It offers similar efficacy as cyclophosphamide in renal remission and survival but a better adverse effect profile in comparison.[8] It is also shown to reduce the risk for failure to induce remission during induction and to reduce the risk of death or end stage renal disease. It is given in the dose of 600mg/m^2/day orally in two divided doses. Adverse effects commonly seen are gastrointestinal (diarrhoea, nausea and vomiting) and infections.

Biologics: Rituximab, an anti-CD20 monoclonal antibody, causes targeted B-cell depletion and has recently been used in the treatment of children with severe SLE resistant to conventional treatment. Evidence so far demonstrates it to be safe and effective as an addition to immunosuppressive therapy in refractory cases.[9] It is given in weekly dose of 375mg/m^2 for about 3-8 weeks. It is associated with a risk of reactivation of dormant infections like hepatitis C, hepatitis B and CMV.

Outcome

The 5 year survival rate for pediatric SLE has been reported to be 95-100% and the 10 year

survival rate to be 86%.[10] Sepsis followed by renal failure are the most common causes of mortality in children. Over last three decades, the outcome has improved dramatically as a result of early diagnosis and aggressive management. Newer biologics will further enhance the prognosis offering effective drugs that allow normal growth, development and fertility in children.

Points to Remember

- ***SLE is an autoimmune, episodic, multisystem disease characterized by remissions and flares.***
- ***Childhood SLE tends to be more severe at onset with higher rate of organ involvement as compared to adult onset disease.***
- ***It is characterized by presence of antinuclear antibodies (ANA). Absence of ANA in a symptomatic patient virtually rules out the diagnosis of SLE.***
- ***Non-steroidal anti-inflammatory drugs, glucocorticoids and anti- malarials are useful in the treatment of patients without major organ involvement. Immuno-suppressive agents like cyclophosphamide, azathioprine and mycophenolate mofetil are used in the presence of major organ damage.***
- ***Newer biologics like Rituximab have proven to be effective in refractory cases of SLE.***

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RHEUMATOLOGY

JUVENILE DERMATOMYOSITIS : A REVIEW

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Abstract: *Juvenile dermatomyositis is the most common of pediatric idiopathic inflammatory myopathies, with an estimated incidence of 2 to 3 per million per year. It principally affects the muscles and skin via inflammation of the small vessels, but may also affect other organs. It is diagnosed on the basis of the criteria set by Bohan and Peter. The following review describes the epidemiology, characteristic clinical manifestations, the pathophysiology and immunology of the disease. The various treatment modalities are also discussed.*

Keywords: Juvenile dermatomyositis, Clinical features, Diagnosis.

Juvenile dermatomyositis (JDM) is a rare, often chronic, multisystem autoimmune disease with onset during childhood, by definition before 18 years of age. It is a systemic vasculopathy, affecting primarily the skin and muscle, causing symmetric proximal weakness and a characteristic skin rash.

Historical perspective

The term dermatomyositis was introduced by Unverricht in 1887 who also described the cutaneous and muscular manifestations of this disease. The first postmortem study that described the classic histopathologic features of the disease in a child was by Batten in 1912. Therapy in the form of glucocorticoids came later in 1950s.[1]

Epidemiology

Juvenile dermatomyositis is the most common inflammatory myopathy of childhood. Various studies report an incidence of 2 to 3 per million per year.[2] Incidence varies according to the region. In India, it constitutes about 3.3% of pediatric rheumatologic disorders seen at a tertiary care center.[3] Dermatomyositis has a bimodal distribution of ages at onset with a peak in the 5- to 14-year-old range, and a second, much larger peak in the 45- to 64-year-old range.[2] The average age of onset in the juvenile form is 7 years, but 25% of children are less than 4 years at onset.[4] Although female children seem to predominate (2:1) in the pediatric JDM population of the United States[5], Europe[6], and China[7] studies from Japan[8] and India[3,9] documented a reverse ratio. The male predominance seen at our center appears to be more apparent than real and is probably a reflection of our societal bias as a result of which more boys are brought to hospital as compared to girls.

Etiological factors

Most studies suggest that JDM is an autoimmune angiopathy.[1] Like other autoimmune diseases, this could result from environmental triggers in the setting of an underlying genetic susceptibility. Specific HLA alleles such as B8,

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DRB1 0301, DQA10501, and DQA10301 are more common in juvenile dermatomyositis. Cytokine polymorphisms including a tumor necrosis factor (TNFα)-308A promoter polymorphism and intronic polymorphisms of the interleukin-1 receptor antagonist are also likely risk factors.[10-14]

Seasonal clustering with the onset of disease suggests an environmental trigger.[15] Additional evidence suggests the presence of an infectious trigger. Several microbes have been implicated; especially group A β hemolytic streptococci (GABHS), and also coxsackie virus B, toxoplasma, enterovirus and parvovirus.[16] A cause and effect relationship, however, has not been established for any of these.

Maternal microchimerism may be important in childhood myositis. Maternal cell chimerism has been reported in more than 70% of T lymphocytes in peripheral blood cells and in 80%-100% of muscle-tissue samples from patients with juvenile dermatomyositis.[17] The presence of chimeric cells of maternal origin may cause graft-versus-host disease or autoimmunity.

Pathophysiology

Both humoral and cellular immunity contribute to the pathogenesis. Cell mediated immunity to muscle antigens (i.e. activated cells) and immune complex disease may participate in pathogenesis.[18] Response of patients' lymphocytes in vitro to allogenic or autologous muscle extracts has been described.[1]

The vasculopathy of juvenile dermatomyositis affects skeletal muscle, skin, the gastrointestinal tract, and other tissues such as lungs, kidneys, eyes, and heart. In the diseased muscle perivascular and perifascicular lymphocytes (B cells and CD4+ T cells) produce immunoglobulin and myocytes increase the expression of MHC class I and II molecules.[19] Complement is deposited in vessels in the muscle and affected skin.[16]

Typical histological changes in the muscle include swelling of the capillary endothelium with obliteration of the lumen, perifascicular atrophy, perivascular inflammation, muscle degeneration and regeneration, and the presence of tubuloreticular inclusions visible by electron microscope. Perifascicular atrophy, in particular, is characteristic of juvenile dermatomyositis.

An international consensus working group has developed a scoring system for muscle biopsies in juvenile dermatomyositis. It describes the following 4 domains:

(1) Inflammatory changes including endomysial, perivascular and perimysial inflammation (2) Vascular changes (3) Muscle fibre changes including MHC class I overexpression, atrophy of perifascicular and other muscle fibres, degeneration or regeneration, and presence of neonatal myosin (4) Connective tissue changes including endomysial and perimysial fibrosis.[20]

Diagnostic criteria

Traditionally the diagnosis of juvenile dermatomyositis is made through a constellation of clinical features and laboratory tests as given in the 1975 criteria by Bohan and Peter.[21]

These criteria include the presence of:

1. Characteristic cutaneous changes consisting of heliotrope discoloration of eyelids with periorbital edema and an erythematous, scaly rash over the dorsal aspects of metacarpophalangeal and proximal interphalangeal joints (i.e. Gottron's papules)

2. Symmetric weakness of the proximal musculature

3. Elevation of the serum level of one or more of the skeletal muscle enzymes: creatine kinase, aspartate aminotransferase, lactate dehydrogenase and aldolase

4. Electromyographic demonstration of the characteristics of myopathy and denervation

5. Muscle biopsy documenting histologic evidence of necrosis and inflammation

In the presence of a characteristic heliotropic rash, a child can be said to have definite disease if 3 of the 4 criteria are fulfilled, probable disease if 2 of the 4 are fulfilled and possible disease if only one criterion is fulfilled.

It should be noted that both the muscle biopsy and electromyography may yield false negative results in some patients probably because of the focal and patchy nature of the disease. With the advent of magnetic resonance imaging (MRI), muscle biopsy is often not considered necessary in most patients.[22] At our centre we no longer carry out this procedure for diagnostic purposes in JDMS if the MRI is supportive.

From the clinical perspective, if a child has a heliotrope rash and proximal muscle weakness, the diagnosis of juvenile dermatomyositis is never in doubt.

Clinical presentation

JDM classically presents with an insidious progression of malaise, easy fatiguability, muscle weakness (especially involving the neck flexors), fever, and rash that may precede the diagnosis by 3 to 6 months. A more acute onset occurs in approximately one third of children.

Both the cutaneous and myopathic manifestations of JDM may be precipitated by sun exposure.[23] Constitutional symptoms start with fever in the range of 38ºC to 40ºC, followed by malaise, easy fatigability, anorexia, weight loss and irritability.

Skin involvement is characteristic.The three most typical manifestations are the heliotrope discoloration of the upper eyelids, Gottron's papules, and periungual erythema with capillary loop abnormalities. Heliotrope rash is seen over the upper eyelids as a violaceous, reddish purple suffusion, often with edema of the eyelids and face. Gottron's papules are symmetrical, scaly, erythematous papules commonly seen over the proximal interphalangeal and metacarpophalangeal (but never the metatarsophalangeal) joints of the hands. The extensor surfaces of the elbows, knees and malleoli may also be involved. The shawl sign is a widespread, flat reddened area that is seen over the upper back, shoulders, and back of the neck. The V sign has an appearance similar to that of the shawl sign, but occurs over the front of the chest in the area of skin exposed by a V-necked sweater. Patients may develop "mechanic's hands", a roughening and cracking of the skin of the tips and sides of the fingers, resulting in irregular, dirty-appearing lines that resemble those of a manual laborer.

Characteristic abnormalities of the periungual skin and capillary bed are present in 50% - 100% of children.[16] The periungual skin is erythematous. The signs of capillary vasculopathy are visualized by nailfold capillaroscopy. This serves as a simple non-invasive means of monitoring disease activity in children with juvenile dermatomyositis.[24] The various techniques for this are the use of a stereomicroscope with microscopic oil, ophthalmoscope with 40+ lens or simply a water soluble gel and a magnifying glass. Telangiectasias, dilataion of isolated loops, thrombosis and hemorrhage, dropout of surrounding vessels, and arborized clusters of giant capillary loops are found. There is associated marked cuticular overgrowth.

Dystrophic calcification (calcinosis) is the deposition of basic calcium phosphate, hydroxyapatite or fluoroapatite crystals. This occurs in upto 30% of patients.[2,23] The sites most frequently affected are pressure points: elbows, knees, digits, and buttocks. Most often this begins 1- 3 years after onset of illness.

Four subtypes have been described: (1)Cutaneous or subcutaneous plaques or nodules. (2)Deposits that extend to muscle. (3)Calcinosis along fascial planes that might lead to contractures and (4)Widespread calcium exoskeleton.

Calcinosis may resolve spontaneously or can lead to skin ulceration, joint contractures, nerve entrapment or local inflammation. Sometimes, the calcific material is extruded through the skin as a white cheesy exudate, leaving behind a dry pitted scar. In severe cases the child may be literally encased within a shell of calcium salts. There is evidence that children who are treated early and aggressively do not develop any soft tissue calcifications. Specifically those children who have a longer interval of time between onset of symptoms and initiation of appropriate therapy are more likely to develop calcinosis. Once initiated, the route and the dose of the therapy used seemed to play a role in averting the development of calcinosis.[23]

Dermatomyositis sine myositis or amyopathic dermatomyositis, which is defined as typical dermatomyositis skin rash without muscle involvement for atleast 2 years, is uncommon. Most of these patients may have a mild muscle disease which may be missed.[16]

Muscle weakness at onset is predominantly proximal. The child has difficulty in climbing stairs, getting up from a chair, combing hair, inability to dress himself, all demonstrating a weakness of limb girdle muscles. Gower's sign is often positive. Neck muscle weakness is an important indicator in JDM. Anterior neck flexors become weak and the child has inability to hold head upright or maintain a sitting posture. This is often the last indicator, either clinical or laboratory, to resolve.[23] Child also complains of muscle pain and stiffness. On examination weakness is symmetric, maximal in the proximal muscles of the shoulders and hips, in the neck flexors, and in the abdominal musculature. Later in the disease the distal muscles of the extremities as well as pharyngeal, hypopharyngeal, and palatal muscles also get affected. Palatal involvement (as manifested by an absent/weak gag reflex) indicates severe disease and mandates a more aggressive therapeutic regimen.

Arthralgia which is transient and nondeforming may involve both large and small joints symmetrically, but if this is very significant or persisting, the possibility of an overlap syndrome needs to be considered.

Lipodystrophy is a recently recognized complication of juvenile dermatomyositis. While clinically this condition may be present in upto 40% of children with juvenile dermatomyositis, assessment by a skin fold caliper may demonstrate loss of subcutaneous fat in upto 65%.[25] It may be complicated by hirsutism, acanthosis nigricans, clitoral enlargement, hepatic steatosis, insulin resistance and hypertriglyceridemia. In our experience, lipodystrophy often goes unrecognized if one is not careful.[25]

Gastrointestinal involvement may be as a result of both the underlying vasculopathy and impairment of muscle function. There is decreased esophageal motility with resultant esophageal reflux. Masseter involvement with chronic masseter atrophy may give a "chipmunk" appearance to the face. Severe vasculopathy may lead to ulceration, perforation, hemorrhage and pneumatosis intestinalis that can affect any part of the gastrointestinal tract. Another clinical

consequence of this is decreased absorption of nutrients and medications associated with weight loss. This may account for the better observed efficacy of parenteral forms of therapy.

Although electrocardiographic abnormalities are not uncommon, clinically significant cardiac involvement is unusual. Myocarditis may lead to asymptomatic conduction abnormalities with occasional complete right bundle branch block.[23,26] Clinically the patient may have non specific murmurs and cardiomegaly. Pericarditis and hypertension have also been reported.[1]

Pulmonary findings include a decrease in ventilatory capacity in the absence of respiratory complaints. Pulmonary fibrosis can occur, but is more common with children who have antibodies to Jo-1.[26]

Ophthalmic involvement may present with thrombosis of vessels at the eyelid margin and "cotton-wool" spots on the retina resulting from small vessel occlusion. Intraretinal edema can cause injury to the retinal nerve fibers and lead to optic atrophy and visual loss.[26].

Renal involvement is secondary to massive breakdown of muscle elements leading to myoglobulinuria and renal failure. Primary renal disease may also occur because cytoplasmic tubular arrays have been found in renal glomerular endothelium.[27] In our experience, this is extremely unusual.

Vasculitis sometimes involve the CNS causing depression and wide mood swings.

Differential diagnosis

JDM needs to be differentiated from juvenile polymyositis, postinfectious myositis, primary myopathies and inflammatory myositis accompanying other connective tissue diseases such as scleroderma or mixed connective tissue disorders. The diagnosis is fairly straightforward in the presence of the characteristic heliotrope rash and proximal muscle weakness. However early in the disease the classic findings may be elusive and a careful assessment is warranted.

Juvenile polymyositis is less common, is associated with both proximal and distal muscle weakness, and does not have significant cutaneous or nailfold abnormalities. Postinfectious myositis will reveal a temporal pattern usually following a viral illness (eg. influenza A and B, Coxsackievirus B) and rarely with other organisms. The primary myopathies include muscular dystrophies, congenital myopathies, myotonic disorders and metabolic myopathies. The differentiation may be tricky in the very young, but clinical course gives the clue.

Myositis is also associated with other connective tissue disorders notably systemic scleroderma and mixed connective tissue disease and, to a limited extent, in SLE and systemic onset juvenile rheumatoid arthritis.

The myositis of JDM can be differentiated from that of other disorders by its severity, greater elevation of serum levels of muscle enzymes and histologic examination of muscle obtained by biopsy.

Laboratory findings

Nonspecific indicators of inflammation such as the erythrocyte sedimentation rate and C-reactive protein level tend to correlate with the degree of clinical inflammation.

Specific laboratory diagnostic studies include:

1. Serum levels of muscle enzymes: These are important both for diagnosis and subsequent monitoring of the response to therapy. The baseline evaluation consists of measurement

of aspartate aminotransferase, creatine kinase, aldolase and lactate dehydrogenase. Serum levels of all muscle enzymes usually decrease 3 to 4 weeks before improvement in muscle strength and rise 5 to 6 weeks before clinical relapse. Changes in creatine kinase levels occur first, often falling to normal range within several weeks of starting therapy; aldolase levels are the last to respond. LDH and AST though relatively less specific, more closely mirror disease activity and best predict the flares of disease.[28]

2. Electromyography (EMG): The ideal way of performing EMG is to place the electrodes in an area where the child has proximal weakness and abnormal muscle signal indicated by MRI or USG, but not at the site of a future biopsy. Characteristic EMG changes of myopathy are seen as membrane instability with increased insertional activity, fibrillations, positive sharp waves, random fiber destruction with decreased amplitude and duration of action potentials.

3. Muscle biopsy: It is indicated in the initial assessment of a child if the diagnosis is in any way uncertain; to evaluate "activity" of the disease, especially late in its course or if histopathological support is required before starting long term steroid or immunosuppressive therapy. The muscle to be biopsied is usually the deltoid or quadriceps. Clinical involvement should be tested by physical examination, EMG or MRI. As has already been mentioned, with the availability of MRI we rarely do muscle biopsies in JDM.

Immunological tests

Antinuclear antibodies, mainly of the speckled variety, have been reported in a variable frequency of less than 10 %[3,29] to as high as 85%.[30] Myositis-specific autoantibodies are seen in about 10% of children with JDMS, the most common being anti-Mi2 antibody.[26] Of significance are the anti-synthetase antibodies of which anti-Jo-1 is the most common, present in upto 5 – 10% of juvenile myositis patients.[16] These children more often develop a more severe disease with arthritis, Raynaud's phenomenon and interstitial lung disease. Assay of myositis specific autoantibodies is usually not required for routine patient management. Myositis associated antibodies occur in variants of JDM, often in association with overlap syndromes.

Von Willebrand factor (vWF) released from the damaged endothelial cells was noted to be increased in active juvenile dermatomyositis in various studies. Serum levels of neopterin, a pteridine derived from activated macrophages, is elevated in about 60% of patients.[26]

Studies have also shown that absolute lymphocyte counts were low in active juvenile dermatomyositis, but the percentage of B lymphocyte counts were significantly increased, with an increase in CD4/CD8 ratio.[31] Such studies are, however, only of research interest.

Imaging studies

MRI is useful in identifying areas of involvement, which is detected by positive T2 images. Studies have shown that MRI detects areas of involved muscle in those children with normal muscle enzymes. MR spectroscopy using P31 can be used to monitor response to therapy, when other indicators have normalized.

Radiography can be useful in indicating edema of muscle and subcutaneous tissue as demonstrated by increased soft tissue density and also to look for extent of calcinosis. Extensive osteoporosis of long bones and vertebral bodies is often detected.

Treatment

Since the 1970s, standard treatment for juvenile dermatomyositis has been early initiation

of high dose daily oral corticosteroids which is continued until clinical and laboratory improvement are evident and then slowly reduced over a 2-year period. Though this has shown to markedly reduce the frequency of calcinosis, many patients suffer from side effects of prolonged steroids. For this reason many adjunctive immunosuppressive therapies have come into picture.

The preferred regimen in our unit is as follows:

1. Intravenous pulse methylprednisolone 30 mg per kg for 3-5 days, followed by oral prednisolone (2 mg per kg per day initially and gradually tapered over 6-9 months). Careful clinical (rather than laboratory) monitoring is mandatory during this time so that the dose of prednisolone can be adjusted accordingly. We prefer daily administration of prednisolone for atleast 4-6 months and move over to an alternate day regimen only after 6 months or so.

2.Methotrexate (15-20 mg per m^2 per week) is started along with corticosteroids. The drug is administered subcutaneously (the preferred route) or orally, once every week. It is generally continued for around 24 months and then tapered. Addition of methotrexate to the juvenile dermatomyositis treatment regimen allows a more rapid tapering of prednisolone. This represents a major advance in the management of this condition.

For the minority of patients who do not respond to the aforementioned regimen, additional options include the following:

(i) Administration of intravenous immunoglobulin 1- 2 gm per kg bolus and repeated at 3 to 4 weekly intervals.(ii)Anti - TNFα agents – infliximab and etanercept (iii)Other immunosuppressive agents like cyclophosphamide and azathioprine

In our experience, however, such therapies are now rarely required. Methotrexate remains the cornerstone of management of JDM. Hydroxychloroquine has been recommended as a steroid sparing agent and as a drug that is effective in treating the dermatitis of JDM.[32] This may be useful as an 'add-on' drug that is particularly effective in children with marked photosensitivity.

Physiotherapy forms an essential part of care in juvenile dermatomyositis. In the active phase of disease gentle passive stretching and splinting is necessary to avoid loss of range of motion. During the healing phase, more intensive physical activity is advocated. Local skin care is important along with sun protection using sun-blocking agents.

If calcinosis is a troublesome complication, various forms of therapy can be tried which include colchicines, aluminium hydroxide, probenecid, diphosphonates, diltiazem, intravenous EDTA and warfarin.[1] We have some experience with the use of diltiazem in such situations.

There are studies to suggest that children with dermatomyositis may require lipid-lowering agents as a part of their initial treatment since many of them go on to develop hypertriglyceridemia and lipodystrophy.[25]

Course and prognosis

The disease course is defined as: (i)"Monocyclic" when the patient is free of all clinical and biochemical signs of disease and off all medications at 24 months after diagnosis. (ii) "Polycyclic" when the patient has recurrence of active disease (as determined by clinical, biochemical, or radiographic features) after a definite remission. (iii)"Chronic continuous" when there is persistent disease or continuation of medications beyond 24 months after diagnosis.[2]

Prior to 1960, outcomes were poor, with up to one-third of patients dying of their illness, one-third developing permanent, severe physical limitations, and one-third recovering completely.[33] Mortality rates have now reduced to less than 10%.[16] Death most often results from sepsis, myocarditis, respiratory insufficiency, pneumonitis or from acute gastrointestinal ulceration and bleeding. Functional disability results mainly from calcinosis and contractures, and may also be due to persistent rash, pain or muscle weakness.

Factors that adversely influence outcome include[1]

Disease related factors: (a) Rapid onset and extensive weakness, (b) extensive cutaneous vasculitis with ulceration, (c) gastrointestinal vasculitis, (d) severe endarteriopathy and infarction in muscle biopsy specimen.

Therapy related factors: (a)Delay in diagnosis and institution of therapy, (b)Inadequate dose or duration of therapy, (c)Minimal initial or longtime response to glucorticoid therapy

Presence of myocarditis, persistent dysphagia, diplopia and dyspnea, especially with weakness of intercostal muscles suggests a poor prognosis.[26]

Points to Remember

- ***A child who presents with a characteristic rash and proximal muscle weakness needs early diagnosis.***
- ***With prompt, aggressive therapy an excellent outcome is possible.***

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RHEUMATOLOGY

CHILDHOOD VASCULITIS

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Abstract: *Vasculitis is often poorly understood. There are four categories of pediatric vasculitis namely, small, medium, large vessel and other vasculitis . A possibility of vasculitis should be suspected in any child presenting with prolonged fever, weight loss, fatigue, fever, rash and arthritis, with or without evidence of multi-organ disease. Henoch-Schönlein purpura is the most common small vessel systemic vasculitis. Purpura, arthritis and abdominal pain constitute the classic triad of Henoch-Schönlein purpura and diagnosis is confirmed by skin biopsy. Symptomatic treatment is sufficient in most patients. There is no significant benefit of corticosteroid in preventing development of renal disease. Less than 1% of patients with HSP develop persistent renal disease. Takayasu arteritis (TA) is a large vessel vasculitis. The disease is described to have 3 types of presentations, namely, pre-pulseless, angiodynia and pulseless phase. Conventional angiography is mandatory to confirm the diagnosis. CT and MR angiography have been proven to be useful. Corticosteroids, immunosuppressives and surgery are still the mainstay of treatment of TA.*

Keywords: *Vasculitis, Henoch-Schönlein purpura, Takayasu arteritis.*

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The term vasculitis is often poorly understood and to a degree misused within pediatric practice. They are a heterogeneous group of conditions with a wide spectrum of clinical manifestations. Almost all of us have clinical experience of handling vasculitis, as Henoch-Schönlein purpura (HSP) is the commonest form of vasculitis. In practice most clinicians use the term, "Vasculitis", to describe serious medical disorders with major complications from sustained inflammation and damage to blood vessels and end organs. However, this is not always true.

There have been two previous classifications of vasculitis. The first, by Zeek in 1952,[1] included hypersensitivity angiitis, allergic granulomatous angiitis, rheumatic arteritis, periarteritis nodosa, and temporal arteritis. In 1992, the Chapel Hill consensus conference on the nomenclature of systemic vasculitis revised the classification of primary systemic vasculitides based on histopathologic changes showing that the vessel wall is the primary target. These entities were differentiated from secondary vasculitides in which vessel inflammation may be prominent but is a phenomenon secondary to other inflammatory processes. Primary systemic vasculitides were subdivided according to the size of the vessel principally involved into large, medium and small-vessel vasculitis.

These criteria were developed for adult patients and are not entirely satisfactory for the pediatric population. For this reason, a 2005 consensus conference was held in Vienna to suggest a classification scheme for the childhood vasculitides to provide a uniform

language and a standardization of approach for the diagnosis and treatment. The proposed classification includes 4 categories of pediatric vasculitis. The first, predominantly large-vessel vasculitis, includes Takayasu's arteritis. The second, predominantly medium-size vessel vasculitis, includes childhood polyarteritis nodosa, cutaneous polyarteritis and Kawasaki disease. The third, predominantly small-vessel vasculitis, is subdivided into granulomatous conditions (Wegener's granulomatosis and Churg-Strauss syndrome) and non-granulomatous conditions (microscopic polyangiitis, Henoch-Schönlein purpura, isolated cutaneous leukocytoclastic vasculitis and hypocomplementemic urticarial vasculitis). A fourth category, other vasculitides, includes conditions that do not easily fall into any of the three categories above or that are secondary to other illnesses (Behcet's disease, vasculitis secondary to infection, malignancy, or drugs, vasculitis associated with connective tissue diseases, isolated vasculitis of the CNS, and Cogan syndrome).[2]

Based on our own clinical data, Henoch-Schönlein purpura is the commonest form of vasculitis in childhood followed by Kawasaki disease, Takayasu arteritis, infection and drug induced vasculitis.

A possibility of vasculitis should be suspected in any child presenting with prolonged fever, weight loss, fatigue, fever, rash and arthritis, with or without evidence of multi-organ disease such as renal involvement (polyarteritis nodosa), or cardiac and skin and joint involvement (Kawasaki disease). Early and accurate diagnosis relies on detailed examination and investigation and wherever possible biopsy of the organs(s) or vessel involved, or angiography to show typical features. A high index of suspicion is paramount as most of these conditions have a fairly non-specific presentation at the outset. Two common varieties of vasculitis, namely Henoch-Schönlein purpura and Takayasu arteritis are discussed in this article.

Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) or anaphylactoid purpura is the most common small vessel systemic vasculitis in children, affecting males twice as frequently as females between 2 and 8 yr of age. A recent 2006 European League Against Rheumatism (EULAR) and Pediatric Rheumatology Society (PReS) classification of HSP include palpable purpura as a mandatory criterion, together with at least one of the following findings - diffuse abdominal pain, predominant IgA deposition (confirmed on skin biopsy), acute arthritis in any joint and renal involvement (as evidenced by hematuria and/or proteinuria).[2]

Clinical features

Purpura, arthritis and abdominal pain are known as the classic triad of Henoch-Schönlein purpura. Purpura occurs in all cases, joint pain and arthritis in 80%, and abdominal pain in 62% cases. Some include gastrointestinal hemorrhage as a fourth criterion, which occurs in 33% of cases, sometimes but not necessarily due to intussusception. The hallmark of the disease is the rash, beginning as pinkish maculopapules on extensor surface of legs and buttocks and progressing to palpable purpura which tend to occur in crops, last from 3–10 days, and may appear at intervals that varies from few days to as long as 3–4 months. In less than 10% of children, recurrences of the rash may occur until as late as a year and rarely, several years after the initial episode. Arthritis is usually localized to the knee and ankle, non-erosive in nature and resolves after a few days without residual deformity. Renal involvement occurs in 25–50% of children and may manifest as hematuria, proteinuria, nephritis or nephrotic

syndrome or acute renal failure. Children with renal involvement at presentation should be examined every 3-6 months because renal failure or hypertension can develop even 10 years after disease onset. Rare complications of HSP include seizures, paresis, coma, mononeuropathies, infarction with bowel perforation, cardiac and eye involvement, pancreatitis, pulmonary or intramuscular hemorrhage, orchitis and testicular torsion.

Investigations

Routine laboratory tests are neither specific nor diagnostic. Affected children often have a moderate thrombocytosis, leukocytosis, high erythrocyte sedimentation rate (ESR), anemia, low factor XIII level and 50% of patients have elevated concentrations of IgA and IgM. Anticardiolipin or antiphospholipid antibodies may contribute to the intravascular coagulopathy. Barium enema or ultrasonogram of abdomen detect intussusception which is usually ileoileal in location. Azotemia and red blood cells, white blood cell casts or albumin in the urine signify renal involvement. Definitive diagnosis of vasculitis is confirmed by skin biopsy.

Treatment

Symptomatic treatment is sufficient in most patients. It includes maintenance of good hydration, nutrition and electrolyte balance, pain control with paracetamol and antihypertensive if necessary. A recent Cochrane review in July 2009 failed to document any significant benefit of corticosteroid in preventing development of renal disease.[3] Systemic steroids are indicated in the following serious situations:

- Persistent nephrotic range proteinuria
- Crescents in more than 50% of glomeruli with RPGN
- Severe abdominal pain
- Substantial GI hemorrhage
- Marked subcutaneous edema
- Severe scrotal edema and orchitis
- Neurologic system involvement
- Intrapulmonary hemorrhage

Prednisolone is used at a dose of 1-2 mg/kg/day for 7 days followed by a gradual tapering over 2-3 weeks. Intravenous pulse methylprednisolone along with immuno-suppressive drugs like cyclophosphamide or azathioprine is recommended in RPGN with acute renal insufficiency. Children with chronic or recurrent HSP also respond to intravenous pulse methylprednisolone (30 mg/kg/day, maximum 1 g/day, daily for 3 days followed by once or twice weekly and tapered in frequency depending on response). The use of mycophenolate mofetil, urokinase, warfarin, intravenous immunoglobulin and plasmapharesis need to be tested before their use is consistently advocated. If anticardiolipin or antiphospholipid antibodies are identified and thrombotic events have occurred, aspirin 5mg/kg given once may decrease the risks associated with a hypercoagulable state.

Prognosis

HSP is a self-limited vasculitic disease with an excellent overall prognosis. Recurrences occur in 50% of patients within 6 weeks but can happen as late as 7 years after the initial disease. The higher the number of recurrences, the higher the likelihood of permanent renal damage. Less than 1% of patients with HSP develop persistent renal disease and less than 0.1% develop end stage renal disease. Persistent heavy proteinuria, hypertension, azotemia and extensive cresents on biopsy indicate poor prognosis. Although rare, death may occur during the acute phase of the disease as a result of bowel infarction, CNS involvement or renal disease.

Takayasu arteritis

Takayasu arteritis (TA) is a large vessel vasculitis and the most commonly involved vessels are the renal artery, subclavian artery, aorta and carotid arteries. Pulmonary arteritis is an important feature of TA that is not found in other forms of vasculitis; its frequency has been reported to be as high as 50%–80% in some series. TA occurs more commonly in female patients (2.5:1 female: male ratio)in the second and third decades of life, but has also been reported in children as young as 8 months of age. The disease is more frequent in Asian and Indian populations and it is the commonest cause of renovascular hypertension in them.

Clinical manifestations

The disease is described to have 3 types of presentations.[4] In the pre pulseless, first phase, manifestations are non-specific and include malaise, fever, headache, arthralgia, myalgia and weight loss. Angiodynia is a feature of the second phase during which the patient experiences pain along the affected vessels. Hypertension, pulselessness and complications of hypertension characterize the third phase. During the pulseless phase, a characteristic bruit, often over the carotid or subclavian arteries, may be present on auscultation. It is important to recognize the disease at an early stage as clinical and angiographic improvement have been achieved by early institution of immunosuppressive therapy. There may be splenomegaly, dermatologic features like erythema nodosum, malar rash and erythema induratum and cardiac involvement like dilated cardiomyopathy, myocarditis, and pericarditis. Uveitis may be a presenting complaint.

Several differences have been observed between pediatric TA and adult disease. Acute symptoms due to hypertension and its complications like congestive heart failure and encephalopathy are the predominant manifestations in children resulting in shorter interval before diagnosis. Symptoms due to limb and CNS ischemia, which are frequent in adults, are seldom reported in children. Abdominal and thoracic segments of the aorta are preferentially affected in children mimicking coarctation of aorta. Aneurysm formation commonly encountered in adult TA is rare in children, though aneurysms in pediatric TA have been reported from India.

TA has been associated with other autoimmune diseases such as systemic lupus erythematosus, juvenile idiopathic arthritis, anterior uveitis, sarcoidosis, seronegative spondyloarthropathy, Crohn's disease, Wegener's granulomatosis, and Sweet syndrome

Diagnosis

Based on EULAR recommendations, the classification of a child having TA requires the presence of angiographic abnormalities plus one or more of the following four newly defined criteria: (1) decreased peripheral arterial pulse (and/or claudication of extremities), (2) arm blood pressure difference of >10 mm Hg, (3) bruits over the aorta and/or its major branches and (4) systemic hypertension.[2] Angiographic abnormalities have been demonstrated traditionally with conventional angiography. This technique is not only invasive, but is not sensitive in early disease. Characteristic findings on angiography include stenosis or aneurysmal dilatation of the aorta, its major branches and the pulmonary arteries. According to the International TA conference in Tokyo 1994 new angiographic classification as follows: type I-affecting branches from aortic archtype IIa-ascending aorta, aortic arch and its branches type IIb-IIa and thoracic descending aorta, type III-thoracic descending aorta, abdominal aorta and / or renal arteries, type IV- abdominal aorta and / or renal arteries type V-combined

features of type IIb and IV. Involvement of the coronary or pulmonary arteries should be designated as C(+) or P(+) respectively.[5] Color-coded Doppler sonography can facilitate an accurate diagnosis of Takayasu arteritis by the characteristic appearance of homogeneous circumferential intima-media thickening of the common carotid arteries.

Definite diagnosis of TA in the acute phase is difficult. The presence of intermittent unexplained systemic symptoms of variable duration in conjunction with an elevated ESR should prompt periodic auscultation of large arteries and blood pressure measurements in all 4 limbs. Besides high ESR, a microcytic hypochromic anemia, leukocytosis and polyclonal hypergammaglobulinemia may be found. Conventional angiography is usually mandatory in the initial evaluation of the disease. However, in recent years noninvasive imaging procedures such as CT and MR angiography have been proven to be useful.[6] Although the luminal changes are well depicted with conventional angiography, mural changes are best evaluated with CT or MR angiography. MR angiography may be particularly useful in detection of early signs of large-vessel disease and has the added advantage of revealing evidence of ongoing vessel-wall inflammation.

Treatment

Corticosteroids are still the mainstay of treatment. In addition, methotrexate, azathioprine, mycophenolate mofetil and cyclophosphamide have been used in treatment of TA. Most authors recommend cyclophosphamide and anti TNFs only for patients with severe TA, refractory to other immunosuppressive drugs.

Anti-platelet agents like aspirin and dipyridamole are used in patients with transient neurological symptoms. Prednisolone is used at 1-2 mg/kg/d for several weeks and tapered over months. Although 60% of patients respond to this treatment, 40% relapse on tapering of steroid. Symptoms of patients who relapse on tapering of corticosteroid may be controlled with weekly infusions of methylprednisolone (30 mg/kg, not to exceed 1 g/wk). Regimens including weekly methotrexate or daily or monthly intravenous cyclophosphamide have been used in individuals with glucocorticoid-resistant TA. Role of intravenous immunoglobulins, recombinant IL-1 receptor antagonists, IL-4 and anti-TNF or rituximab are yet to be established

Percutaneous transluminal angioplasty (PCTA) is the commonest palliative procedure performed with a success rate varying from 56 - 80%. Re-stenosis can occur and surgical bypass procedures like splenorenal and aortorenal shunting become imperative when stenosis exceeds 70%. Irrespective of the surgical procedure undertaken, the outcome appears to be favourable when the disease is quiescent. Indications for surgical repair or angioplasty are renovascular stenosis, coronary artery stenosis, extremity claudication, cerebral ischemia and/or critical stenosis of 3 or more cerebral vessels, aortic regurgitation, thoracic or abdominal aneurysms larger than 5 cm in diameter and severe coarctation of the aorta. An association with tuberculosis has been described but not proven. The high incidence of previous and present active tuberculosis suggest that tuberculosis may play an important role in the eitology of TA.[7,8] However, treatment for tuberculosis is not justified in all cases until the exact role of tuberculosis in well established.

Prognosis

More than 50% of cases achieve remission after the 1st course of therapy, but about 25% of cases never achieve remission. The most dreaded complication of this often fatal illness is an

arterial aneurysmal rupture. The 5-yr mortality has been reported to be as high as 35% to 40%. It is therefore important to have a high index of suspicion and in doubtful cases a low threshold for diagnostic evaluation.

Points to Rembember

- ***There are four categories of pediatric vasculitides.***
- ***Henoch-Schönlein purpura and Takayasu arteritis are the two common conditions among pediatric vasculitides.***
- ***Symptomatic treatment is sufficient in most of the patients with HSP.***
- ***Early diagnosis and institution of immuno suppressive therapy are essential for optimal outcome in Takayasu Arteritis.***

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NEWS AND NOTES

ALMANAC 2010

Ninth Winter Symposium of CMC, Vellore

on **"Biology of Childhood Disease"**

Date: 6th, 7th & 8th January, 2011

For undergraduates, postgraduates and paediatricians interested in clinical and basic science research

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RHEUMATOLOGY

ARTHRITIS MIMICKS IN CHILDREN

*** Balameena S**

Abstract: *Children present with joint disabilities during the growth period and many factors contribute to it.*

Keywords: *Arthritis, Noninflammatory, Hypermobility.*

Amongst children there may be over perception of pain because of the anxiety of parents. It is therefore pertinent to know the various disorders simulating inflammatory arthritis.[1]

Description

Non inflammatory joint pain involves one or few joints with minimal or no early morning stiffness. It may be due to bony, bursal and tendon sheath swelling and may be localized to one part of the joint or periarticular structures. Warmth and post inflammatory pigmentation are absent. Good response to analgesics is often noticed.

Clinical presentation

In general, growing children present with:

Neck pain: Abnormal reading posture, cervical lymphadenitis and muscle spasm are few causes.

Shoulder pain: Sports activity like baseball can cause strain of proximal physis with widening in the humerus which is called as "Little League Shoulder"

When there is apophysitis of the medial epicondyle, it is "Golfer's elbow" while that of lateral epiocondyle, it is "Tennis elbow".

Hip pain: Femoral osteomyelitis, sickle cell anemia and hip dysplasia may mimic arthritis of hip.

Anterior knee pain: Chondromalacia,Osgood Schlatters, osteochondroses are the conditions that present with knee pain.[2]

Shin pain: Growing pain of childhood and shin splints frequently cause parental concern.

Feet pain: Pes planus, tarsal bone anomalies minor malalignment in talipes tendon insertion, lead to pain in feet.

Back pain: School bag strain and faulty sitting posture are the main causes of back pain.[3]

Specific differential diagnosis

1. Benign hypermobility of childhood: Generalised hypermobility of joints with or without congenital abnormality of connective tissue.[4]

Hyper mobility syndromes with congenital abnormality of connective tissue ground substance are Marfan's, homocystinuria, Stickler's, Ehler-Danlos, Osteogenesis imperfecta, William's and Down syndrome.

Beigtons scale and modified Carten and Wilkinson's scale are used to assess the hypermobile joints without obvious congenital abnormality.

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Females are affected more than males. Positive family history of frequent trips and falls with hypermobile joints will be elicitable.

Modified criteria Carter and Wilkinson

Three of the following five criteria are required to establish a diagnosis of hypermobility

Touch thumb to volar forearm

Hyperextend MCP joint so finger is parallel to forearm

>10% Hyperextension of elbow

>10% Hyperextension of knees

Touch palms to floor with knees straight

Beighton's scale

The criteria are as above.

2 for each criterion on both sides - 8

1 for the last criterion

> 6 points out of 9, define hypermobility

Other criteria

Put heel behind head

Excessive internal rotation of hip

Excessive extension of the foot

Passively touch elbow behind the back

Amongst age group < 4 years, 50- 60 % are hypermobile and above 10 years atleast 10 -20 % remain hypermobile throughout their life time. Wrist and feet pain (ligament strain and pes planus), anterior knee pain (chondromalacia) and backache are common in these children. Other features are out toeing, hyperpronated foot and genu recurvatum.

Complications are effusions and frequent school absenteeism due to ligamental sprains and strains. Treatment includes reassurance and supportive orthotics.

2. Chondromalacia patella: Seen in adolescent females who develop pain on flexion of knees (theatre sign) and in squatting posture. This is due to patellar tendon strain because of softened patella.

3. Shin splints : Frequent jogging leads to friction at the insertion of the soleus muscle producing periosteitis.[5]

4. Osgood Schlaters disease: Traction apophysitis. Common in males. Usually seen as a tender swelling of the infrapatellar area which is due to avascular necrosis in the tibial tuberosity. Similar disorders of avascular necrosis can occur in other bones also: In spine Sheuermann's disease, Navicular-Kohler's. Second metatarsal head - Freiberg's, Proximal inter phalangeal joints of hand and of the first toe –Thiemann's disease.

5. Growing pain: Benign nocturnal pain of childhood.[8,9] 10 -20% develop pain in the thigh and calf areas during evening and night hours disturbing their sleep. It is precipitated by undue exercises and physical excursions following sports activity. Reasurrance and massaging, will help.[6]

6. Osteo chondritis dessicans: In this condition there is separation of cartilage and bone in the femoral condyle leading to articular cartilage loss. It is produced due to repeated activity related pain . Complications like effusion can occur. Rest and quadriceps strengthening exercises are recommended.

7. Progressive pseudo rheumatoid arthritis: Due to familial laxity of ligaments and tendons the deformity mimics rheumatoid arthritis and is progressive to produce disability of finger joint functions.

8. Metabolic bone diseases : Mucopolysaccharidosis—Children with Morquio's disease will have many bony and joint deformities. These would ressemble that of inflammatory arthritis, but produced due to mechanical causes of bony enlargement and stretching of tendon sheath.

9. Dysplasias: Epiphyseal and physeal dysplasia produce bony enlargement and thereby present as joint deformities and early osteoarthritis .

10. Plica thickening: Causes patella femoral pain syndrome, common in male. This is characterised by insidious onset. The mechanism is tendon stretch over superomedial border of femoral condyle.

11. Osteochondroses: Avascular necrosis in the ossification centre seen frequently in male. Common in femoral condyle.

12. Legg-Calve Perthes disease: Children present with limp on one side and later opposite side. Prognosis is favourable when age is below 6 yrs and if less than half of the epiphysis is affected. If larger area of epiphysis is involved they progress to degenerative arthritis in adult life.[7]

13. Patello femoral pain syndrome: This is more common in females. Insidious onset, seen when walking down stairs. Knee strapping along with vastus medialis exercises would help.[8]

14. Malignant conditions: Acute lymphatic leukemia can present with severe joint pain with no apparent swelling with continuous fever. Osteoid osteoma are benign tumors which present with nocturnal pain resembling bone and joint pain but promptly relieved with analgesics.

Lymphomas, neuroblastoma, osteosarcoma, Ewings sarcoma with secondaries present with bone pain.

15. Arthrogryphosis: These are heterogenous group of sporadic disorder of unknown cause. Stiffness and contracture of joints presenting with widespread flexion contracture and dislocation with marked reduction in the subcutaneous tissue and muscular atrophy around the joints are noticed.Physiotherapy and correction of deformities are to be planned.

16. Somatoform disorder: Is common in children as increasing school pressure and bullying abuse are the underlying situations, which the parents have a role to recognize. Appropriate measures have to be taken towards protection of child's mental well being.

17. Idiopathic pain syndromes: Chronic regional pain syndrome (CRPS II) is uncommon in children. Excruiciating pain,hypersensitivity to light touch, coldness and cyanosis with refusal to use the limb are present.[9]

18. Spinal pain: Can be organic as in discitis, osteomyelitis and cord compressions. Spondylolisthesis and stress fractures may be seen in juvenile osteoporotic vertebra commonly in the lower lumbar levels.[10]

Points to Remember

- ***In the scenario of childhood joint disability, it is important to rule out congenital abnormality of connective tissue and joint diseases which can produce limitation of joint movements.***

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RHEUMATOLOGY

AUTOANTIBODIES IN PEDIATRIC RHEUMATIC DISEASES

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Abstract: *Systemic autoimmune rheumatic diseases are characterized by the production of autoantibodies directed against various cellular constituents. These autoantibodies are closely associated with certain diseases and clinical manifestations. Therefore they are useful for clinical practice to diagnose disease and to predict clinical subsets of disease activity and prognosis. This article reviews the role of autoantibody testing and a practical approach to use these tests in day today practice.*

Keywords: *Autoimmune, Rheumatic diseases, Autoantibodies.*

Systemic autoimmune rheumatic disorders are one of the differential diagnoses in evaluating any chronic childhood illness because of their protean manifestations. In most of the autoimmune diseases, a humoral immune response is characteristically seen, with autoantibodies directed to distinct intracellular antigens. This phenomenon can be shown in autoimmune diseases like systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM), mixed connective tissue disease (MCTD), systemic sclerosis (SSc), Sjogren's syndrome (SjS) and polymyositis (PM). The evaluation of a child with a potential systemic autoimmune disease involves the use of immunologic testing for autoantibodies.

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The measurement of autoantibodies offers numerous clinical utilities:

1. Marker of diseases: Most autoantibodies have high disease specificity and therefore have a diagnostic value if they are positive.

2. Marker of disease subsets: Most autoantibodies are associated with certain subsets or clinical symptoms of each disease (i.e. anti dsDNA and lupus nephritis, and anti-Jo-1 and myositis with interstitial lung disease).

3. Marker of disease activity: Some autoantibodies are closely correlated to the disease activity (i.e. anti-dsDNA titers in SLE, and C-ANCA titers in Wegener's granulomatosis).

4. Marker of prognosis: Certain autoantibodies can be useful to predict the prognosis or severity of diseases (i.e. anti-SRP and severe polymyositis, anti-RNA polymerases and renal crisis in scleroderma).

In last few decades, the magnitude and complexity of autoantibody tests has grown greatly to the point that there is frequent confusion and misunderstanding of which tests to order, when to order them and then how to interpret the results.[1] A practical approach to the use of autoantibodies in the diagnosis and management of systemic autoimmune diseases is discussed in this article.

What should be known before ordering the autoantibody test?

Autoantibodies are group of biomarkers that may help to establish a diagnosis and prognosis. Other biomarkers include serum complement

(i.e. C3, C4), cytokines (i.e. tumor necrosis factor, interleukins) and acute phase proteins (i.e. C-reactive protein) which can be useful and important to establish a diagnosis and follow disease activity. Autoantibodies testing should only be performed in the setting of clinical suspicion of a autoimmune rheumatic disease. It should not be used to screen asymptomatic individuals because they are commonly found in clinically normal and asymptomatic individuals, particularly in first degree relatives of autoimmune rheumatic disease patients. In addition, the prevalence of autoantibodies increases with age and other conditions such as infections (tuberculosis, malaria, subacute bacterial endocarditis and viral illnesses), malignancies and non-autoimmune inflammatory diseases.[2] Last, the interpretation of autoantibodies results has become more complex in light of emerging evidence showing that certain autoantibodies can antedate clinical expression and diagnosis of conditions such as systemic lupus erythematosis (SLE)[3, 4] and rheumatoid arthritis (RA).[5]

When to order autoantibody test?

Test with high sensitivity (proportion of patients with the disease who have a positive result) should be used for screening whereas tests with high specificity (proportion of patients without a disease who have a negative test result) should be used for confirmation of diagnosis. Mere presence of an abnormal antibody does not mean disease. Simple and practical approach to autoantibody testing[6] and a summation of a suggested approach is shown in Figs. 1 and 2. It should be stressed that in many cases it is not necessary to proceed to specific testing when the autoantibodies screening test is negative. For example, it is not necessary to order anti-DNA, anti-Sm, anti-RNP or anti-chromatin if the screening autoantibody such as antinuclear antibody (ANA) is negative. It is also important to recognize that not all disease-related autoantibodies are detected by a screening test. These include ribosomal P antibody seen in SLE and Jo-1 antibody seen in JDM. There are multiple commercial autoantibodies kits that are widely used as an approach to screening, detecting, defining and quantitating serum autoantibodies.[7] But the most common in use today are those that rely on autoantibody detection by indirect immunofluorescence (IIF) on tissue culture cell substrates such as HEp-2 cells and enzyme linked immunoassay (ELISA). Table.1 gives the various methods used in autoantibody estimation with their advantages and limitations. Serology Sub-Committee of International Union of Immunology Societies (IUIS) recommend that the autoantibodies by IIF are currently the test of choice for screening patients with symptoms compatible with systemic autoimmune rheumatic disease.[8] Thus, if the lab uses the ELISA, the physician must be aware of the potential of a "false-negative" result.

How to interpret autoantibodies results?

ANA is a good screening test if you suspect autoimmune rheumatic disease**s.** Results of the ANA test are usually reported as both a titer and pattern, both of which are important in the interpretation of the test. The ANA titer can be useful in making a diagnosis, but should not be used to monitor disease activity. In general, higher titer values are more likely to represent true-positive results. Titers of 1:160 and above are considered positive and patients may require further diagnostic workup. In many clinical laboratories, titers of 1:80 or less are equivocal and nonspecific. However, these generalities have caveats. In children, an ANA of 1/20 or even 1/40 may be important in context of clinical symptoms and further analysis of the specificity is usually required. A positive ANA result is also reported with a pattern that reflects the

Table 1. Common attributes of individual assay technologies used

Assay	Problems	Advantages	Result
Indirect Immunofluorescence - rodent tissue	Subjective, Ro may be missed, semiquantitative, pattern not diagnostic, cannot detect cell cycle related patterns, not specific	Cheap, can be isotype specific	Semiquantitative end point titration or qualitative result at screening titer
Indirect Immunofluorescence - HEp-2	Subjective, Ro may be missed, Semiquantitative (poor precision), pattern not diagnostic, not specific pattern	Cheap, recombinant Ro 60 expression to boost Ro sensitivity available, can be isotype specific	Semiquantitative end point titration or qualitative result at screening titer
Ouchterlony double diffusion	Slow, crude antigens, subjective, qualitative, requires experience, not isotype specific, some false negatives	Specific, cheap	Positive or negative + antigen specificity
Countercurrent Immunoelectrophoresis	Slow, crude antigens, semiquantitative, requires experience, not isotype specific, some false negatives	As double diffusion, but more sensitive	Positive or negative + antigen specificity
Haemagglutination titer	Detects IgG and IgM, semiquantitative, subjective, detects low affinity antibodies	Cheap	Positive or negative + semiquantitative
Immunoblotting (IB)	Qualitative, may be insensitive for Ro, crude antigen, labour intensive	Sensitive, very specific for individual antigens	Positive or negative + antigen specificity
Immunoprecipitation (Farr)	Radioactive, labour intensive, expensive, technically difficult, no isotype specificity, false positivity	Quantitative, high specificity, detects high affinity antibodies	Quantitative result
ELISA	Detects low affinity antibodies, needs high purity well defined antigens (native *v* recombinant), false positivity	Sensitive, variable, can be polyspecific or IgG specific	Qualitative or quantitative results

Table 2. ANA pattern by immunofluorescence and clinical association

IF pattern in Hep2 cells	Autoantibody association	Clinical association
Homogeneous/ diffuse	dsDNA, histones	SLE, DIL, SSc, AICAH many non-pathological ANAs
Speckled Coarse Fine	 RNP/Sm, Ro/La	 SLE, MCTD SLE, SSc, SjS, MCTD, SCLE, NLS
Peripheral/rim	dsDNA, laminin, nuclear pore	SLE, APS
Centromere	Centromere A, B, C kinetechore proteins	CREST syndrome, lcSSc
Nucleolar	Scl-70, PM-Scl	SSc, overlap syndromes
Cytoplasmic	Ro/La	PM, DM, SLE, SjS, PBC, SSc

Abbreviations: SLE: systemic lupus erythematosus, SSc: systemic sclerosis, SjS: Sjögren syndrome, MCTD: mixed connective tissue disease, SCLE: subacute cutaneous lupus erythematosus, NLS: neonatal lupus syndrome, AICAH: autoimmune chronic active hepatitis, APS: anti-phospholipid syndrome, SSc: Systemic scleroderma, DIL: drug-induced lupus, DM: dermatomyositis, lcSSc: limited cutaneous SSc, PM: polymyositis, RP: Raynaud's phenomenon, PBC: primary biliary cirrhosis

intracellular target of the autoantibody. The most common ANA patterns reported are nucleolar, cytoplasmic and nucleoplasmic.[9] The autoantibody pattern can give clues to possible disease conditions and underlying autoantibodies (Table.2). Caution is required here because the problem of the "normal" person who have positive autoantibody may be plagued by years of the false notion that they have a disease where, despite long term follow-up, an autoimmune disease is not evident. This must be balanced by more recent knowledge that positive autoantibodies can antedate disease by many years and hence, are predictive of disease.[4] When specific autoantibodies are reported, inferences about disease associations can be made (Table.3), but because of limitations of autoantibodies testing as sole criteria for diagnosis, it is suggested that the clinician should rely on published classification criteria for various systemic autoimmune disease before advising the patient that they have a autoimmune disease or not. It is important to note that autoantibodies are only markers of disease and are not considered "gold standard" tests for diagnosis of rheumatologic diseases. When the ANA by IF test is positive, subsequent tests to detect specific autoantigens are usually warranted. These include antibodies directed to dsDNA, SS-A/ Ro, SS-B/La, Sm, U1-RNP, Scl 70, Jo-1, chromatin, histone and ribosomal P protein (Figs. 1 and 2). Individual laboratory

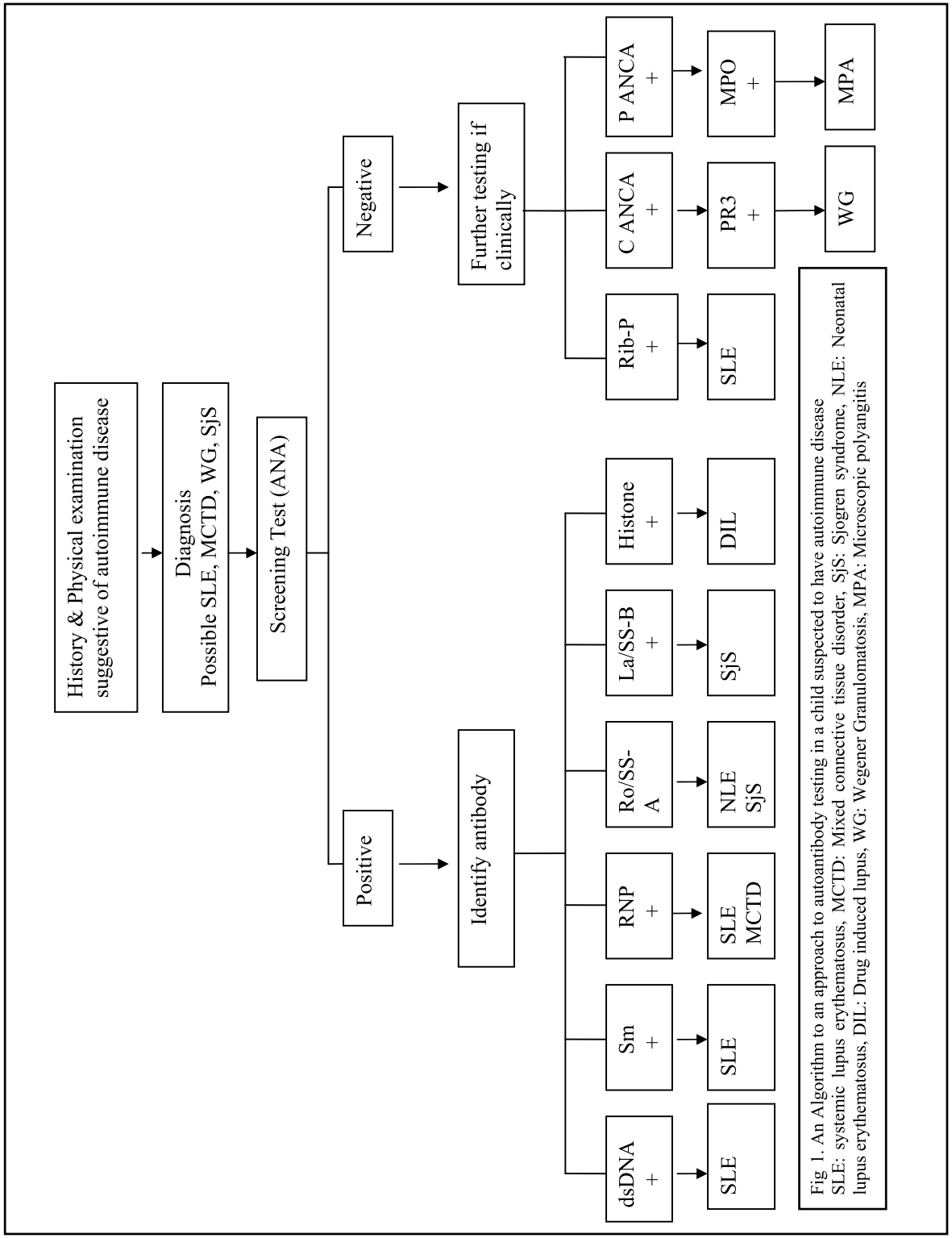

Fig 1. An Algorithm to an approach to autoantibody testing in a child suspected to have autoimmune disease
SLE: systemic lupus erythematosus, MCTD: Mixed connective tissue disorder, SjS: Sjogren syndrome, NLE: Neonatal lupus erythematosus, DIL: Drug induced lupus, WG: Wegener Granulomatosis, MPA: Microscopic polyangitis

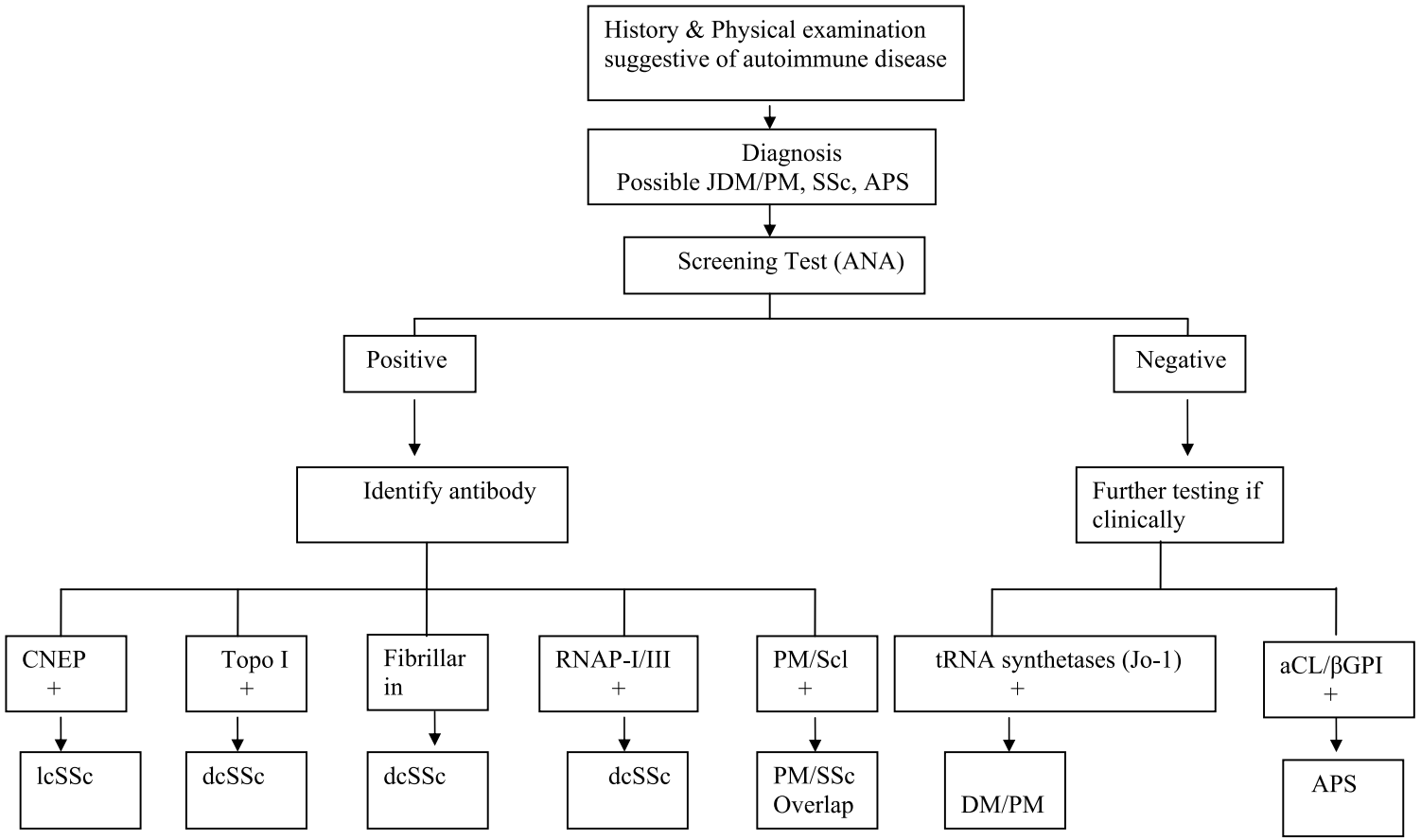

Fig.2. An Algorithm to an approach to autoantibody testing in a child suspected to have SSc , PM/DM or APS.

LcSSc:Localised Scleroderma, dcSSc:Diffuse scleroderma, PM:Polymyositis, APS:Antiphospholipid syndrome, RNAP: RNA polymerase I, II, III, aCL:Anticardiolipin, βGP1:β2 glycoprotein I, CNEP:anti-centromere.

Table 3. Common autoantibodies in systemic autoimmune rheumatic diseases and their clinical significance

Antibodies	Technique	Nature of target antigens	Frequency	Clinical significance
1. Autoantibodies in SLE				
Anti-dsDNA	ELISA/CLIF/Farr	dsDNA	60-70%	Nephritis, disease activity
Anti-Sm	ELISA/IP	U1, U2, U4/U6	25-30%	Highly specific
Anti-U1-RNP	ELISA/IP	U1snRNA	30-40%	SLE, Raynaud's phenomenon
Anti-ribosmal P	IB/ELISA	P0, P1, P2 (60 S subunit)	10%	CNS lupus, disease activity
Antihistone antibody	IB/ELISA	DNA-histone complex	40-50%	Drug induce lupus, disease activity
Anti SS-A/Ro	ELISA/IB	Y1-Y5RNAs (60 k/52 kDa)	25-30 %	Neonatal lupus, SCLE, Sjogren syndrome
Anti SS-B/La	ELISA/IB	RNA polymerase III termination factor (48 kDa	20-30%	Recurrent annular erythema
Anticardiolipin	ELISA		16-60% of SLE	Anti-phospholipid syndrome
β2-glycoprotein	ELISA		15-25% of SLE	(recurrent thrombosis, abortion)
Lupus anticoagulant	APTT, DRVVT		40-50% of SLE	
2. Autoantibodies in SSc				
Anti -Scl-70 (Topo I)	ELISA/IB	DNA topoisomerase I	50 %	Diffuse scleroderma
Anti-centromere	ELISA/IB	Centromere proteins A, B, C	70%	Limited scleroderma
Anti-RNA polymerases	ELISA/IB	RNA polymerase I, II, III	6-24%	Diffuse scleroderma, renal crisis
3. Autoantibodies in myositis				
Myositis specific autoantibodies				
Anti ARS	DD/IP/Western			
Anti Jo-1	Blot	Hystidyl-tRNA synthetase (50 kDa)	15-20%	Anti-synthetase syndrome
Anti PL-7		Threonyl-tRNA synthetase (80 kDa)	<5 %	(myositis, interstial lung disease, polyarthritis
Anti- EJ		Glycyl-tRNA synthetase (75 kDa)	<5%	mechanic's hand, RP)
Anti-OJ		Isoleucyl-tRNA synthetase	<5 %	
		(multienzyme complex)		Severe, refractory Polymyositis
Anti-SRP		Signal recognition particle	5-10%	Dermatomyostiis, good prognosis
Anti-Mi-2		helicase family protein (218 k/240 kDa)	15-20%	
Myositis associated autoantibodies		Ul-snRNP (mRNAsplicing factor)	100% of MCTD	MCTD, non-renal SLE, RP
Anti- U1RNP	ELISA/DD	U2-snRNP (mRNAsplicing factor)	10-20%	SSc-PM overlap
Anti- U2RNP	ELISA/DD	Nucleolar protein complex (110-20 kDa)	8-10%	SSc-PM overlap in Caucasians
Anti-PM-Scl	IP			
5. Autoantibodies in vasculitis				
C-ANCA	IF	Neutrophil proteinase-3 (PR3)	50-80%	Wegener's granulomatosis
P-ANCA	IF	Neutrophil myeloperoxidase (MPO)	30-50%	Microscopic polyangiitis,
	PR3, MPO-ELISA			Churg-Strauss syndrome
6.. Antibodies in Juvenile idiopathic arthritis (JIA)				
Rheumatoid factor	IF	Fc fragment of Ig G	10% of JIA	Present in chronic infection, other autoimmune disease, erosive arthritis
Anti CPP	ELISA	Cyclic citrullinated peptide	5 %	Positive in RF + JIA

Abbreviations: IF: immunofluorescence, IB: Immunoblotting, IP: Immunoprecipitation (Farr), Ouchterlony double diffusion (DD), ELISA: Enzyme linked immunosorbent assay, CIE: countercurrent immunoelectorphoresis, CLIF: Crithidia luciliae IF, SLE: systemic lupus erythematosus, SSc: systemic scleroderma, PM: polymyositis, ARS: aminoacyl-tRNA synthetase, snRNP: small nuclear ribonucleoprotein, SCLE: subacute cutaneous lupus erythematosus, MCTD: mixed connective tissue disease, CNS: Central nervous system, APTT: activated partial thrombolastin time, DRRVT: dilute Russell viper venom test

centers will have different methods for testing these specific autoantibodies. The results from these tests can be more informative than the ANA by IF alone because many of these autoantibodies are disease specific (Table 3).

How to follow-up and when to repeat testing for autoantibodies?

A common question is, "How often or how soon autoantibodies test should be repeated?" In general, autoantibodies testing should be primarily used for initial testing. With a few exceptions, autoantibodies generally do not have value as indicators of disease activity and it is not recommended that a patient be retested unless there is a change in the clinical status that might have implications for a changed diagnosis and/or therapy. Of these exceptions, anti-dsDNA for SLE nephritis, anti-cardiolipin and related antibodies for antiphospholipid syndrome and ANCA for systemic vasculitis are the best documented to have a correlation with disease activity and even rising titers can antedate clinically detected flares. However, it should be noted that some of these autoantibody-disease activity correlations are not without some controversy. In the clinical setting with the use of a wide variety of autoantibody assays, it is very common and inevitable to find "borderline" or "low positive" results. This is attended by the physician's decision of if and when to order a repeat test. The assumption that a low positive test is clinically insignificant should be carefully considered because not all autoantibodies give high binding values or test results in all assay platforms. Considering the welfare of the patient, the best decision is to repeat the test in 6–12 months if the patient is stable or sooner if symptoms and signs escalate. An option is to do repeat testing in cases of borderline results obtained by one technique using an alternative technique (if available). It is important for the physician to appreciate that the cost effectiveness of not repeating a test and, hence, missing an early diagnosis.

Points to Remember

- ***A positive autoantibody test on its own is not sufficient enough for the diagnosis of autoimmune rheumatic disease. These tests must be used in conjunction with history and physical examination.***
- ***Emerging evidence indicates that autoantibodies can antedate clinical symptoms and diagnosis. Therefore, follow-up of the autoantibodies positive individual must be carefully considered.***
- ***Autoantibodies test results are not necessarily the same when done in different laboratories.***
- ***It is not necessary to repeat an autoantibodies test unless it was negative and symptoms have increased or changed.***
- ***Serial autoantibodies tests to follow autoantibodies titers as a measure of disease activity or flares are rarely helpful.***

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CLIPPINGS

Carl Lückhoff, Mike Starr. Minor head injuries in children – an approach to management. Australian Family Physician 05/07/10.

A careful history including time of injury, the mechanism of injury, and any loss of consciousness or seizure activity; a thorough examination including a Glascow Coma Scale (GCS) score; and observation should be appropriate for most patients. Only a small number of injuries require further examination/imaging with computerised tomography. Indicators for transfer to hospital include GCS equal to or less than 12, focal neurological deficit, clinical evidence of skull fracture, loss of consciousness for more than 30 seconds, ataxia, amnesia, abnormal drowsiness, persistent headache, seizure following initial normal behaviour or recurrent vomiting. Postconcussive symptoms frequently occur after minor head injuries and parents and other family members should be aware of what symptoms to expect, and possible duration. Regular follow up until all symptoms have resolved is mandatory, with clear guidelines for stepwise resumption of physical activity.

MajorKarnail SinghM. S. Pannu, Palwinder Singh and Jaswinder Singh. Effect of wheat grass tablets on the frequency of blood transfusions in Thalassemia. Indian Journal of Pediatrics February, 2010.

Forty patients of Thalassemia Major children were treated with wheat grass tablets (WGT). The mean hemoglobin in the pre WGT was 8.54 +/" 0.33 g% whereas in WGT period was 9.13 +/" 0.14 g% ($p < 0.001$). Wheat grass has the potential to increase the Hb levels, increase the interval between blood transfusions and decrease the amount of total blood transfused in Thalassemia Major patients.

GENERAL ARTICLE

APPROACH TO A DYSMORPHIC CHILD

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Abstract: *Though great heights are being reached in molecular diagnostics of genetic diseases, the first step in the approach to a dysmorphic child still is clinical. Without a good initial clinical diagnosis, no amount of investigations would be able to succeed in differentiating the myriad of conditions that are possible in a child with multiple anomalies. A structured and meticulous approach is necessary for delineation of the ever growing list of syndromes. This review aims to give a succinct summary of the pathogenesis and approach to the various congenital anomalies and hints on the newer advances and management of these conditions.*

Keywords: *Congenital abnormalities, Syndrome, Genetic diseases, Anomaly.*

"If it were not for the great variability among individuals, medicine might as well be a science and not an art." - Sir William Osler, 1892. This famous quote probably represents the field of dysmorphology more than any other field in medicine. The subject of dysmorphology which began as something that aroused curiosity among men, sometimes even fright; has gone on to be a clinical art of diagnosis now even to an extent that it has become a definite science venturing into treatment modalities.[1] Dysmorphology is a word coined by Dr.David.W.Smith in 1966 and is derived from the Greek words "dys" (disordered, abnormal) and "morph" (shape, form).[2] In other words it is the study of human congenital defects – abnormalities of body structure that originate before birth. Although the present review deals mainly with clinically recognizable external defects, the reader has to keep in mind that many of the congenital defects are associated with internal defects with most of them having an underlying genetic etiology.

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The need for the field of dysmorphology

Individual birth defects are rare, but, in the aggregate, they account for a large proportion of childhood mortality and morbidity. More than 4000 dysmorphic, multiple congenital anomaly and mental retardation syndromes have been reported with more being added on a frequent basis.[3] 1-3% of children are born with multiple or serious congenital defects. An adequate knowledge and expertise is needed not only for identification of these serious defects but also other minor anomalies which may be clues to a more graver underlying pathology. Prompt recognition of the condition helps in prognostication, investigations, treatment and most of all to give the dreaded recurrence risk.

Classification of dysmorphic defects

It is probably impossible to know all the congenital defects and the associated conditions by heart, hence it is necessary to categorize them into manageable subdivisions. A dysmorphic feature or anomaly is an abnormality of shape,

size or structure. These features are traditionally classified as a major or minor anomaly.[4] A major anomaly is one that has severe medical or cosmetic consequences, such as a congenital heart defect or a cleft lip. A minor anomaly represents a medically insignificant deviation from normal development, such as wide-set eyes or a single palmar crease. Table 1 lists the common minor anomalies used in syndrome delineation. Three or more of these minor malformations are associated with multiple major anomalies in 90% of the patients and hence warrants a thorough evaluation.[5] Before ascribing an anomaly to be significant an astute clinician should first take into consideration the ethnic background and the familial occurrence.

Based on the pathogenesis birth defects can be classified as follows.[4]

- **Malformation** – Early embryological developmental error (eg. cleft palate)
- **Deformation** – Internal or external mechanical forces alter normally forming structure (eg. club foot)
- **Disruption** - Breakdown of a previously normal tissue (e.g. amniotic band sequence) (Fig.1)
- **Dysplasia** – Abnormal cellular organization within a tissue resulting in structural changes (eg. achondroplasia)

When multiple birth defects are encountered it is useful to classify them first in order to arrive at an appropriate diagnosis. The most commonly used system for classification is as follows.[4]

- **Syndrome ("running together" in Greek)** – A pattern of features, often with a unifying underlying cause, that arise from several different errors in morphogenesis. (eg. Down syndrome). Most dysmorphic syndromes are a constellation of major and minor anomalies. The presence of only one feature is never diagnostic but the unique combination gives rise to the syndrome.
- **Sequence** – A pattern of multiple anomalies derived from a single prior anomaly or mechanical factor. For example in case of the Pierre-Robin sequence (micrognathia,

Table 1. Commonly encountered minor anomalies

Craniofacial	Skin	Other body areas
Up and down slanting palpebrae	Aplasia cutis congenital	Clinodactyly
Anteverted nares	Various nevi	Single palmar crease
Posteriorly rotated ears	Cafe au lait spots	Shawl scrotum
Open metopic sutures	Hypopigmented patches	Supernumerary nipples
Ocular heterochromia	Skin syndactyly	Single umbilical artery
Micrognathia	Pigment streaking	Excess nuchal skin
Preauricular pits or tags		Deep sacral dimple
Epicanthic folds		
Hypo/Hypertelorism		

glossoptosis and u-shaped cleft palate), the primary anomaly is the early mandibular hypoplasia which results in a posteriorly located tongue (secondary anomaly) thereby impairing the closure of palatal shelves resulting in a cleft palate (tertiary anomaly) (Fig.2).

- **Association** – Non-random tendency of some malformations to occur together more commonly than would be expected by chance, without being part of a syndrome. (e.g. VACTERL association (vertebral defects, anal atresia, cardiovasuclar anomalies, tracheoesophageal fistula, esophageal atresia, radial dysplasia, renal dysplasia, limb defects)

Approach to a child with multiple anomalies

History

Personal/family history

1. Three generation pedigree chart using standard symbols

2. Elderly mother - chromosomal aneuploidy (e.g. Down syndrome)

3. Elderly father - new autosomal dominant mutation (e.g. achondroplasia, Marfan syndrome)

4. Maternal disease -known associated fetal abnormalities (e.g. sacral agenesis with maternal diabetes)

5. Poor social history - Possible alcohol/ drug ingestion

6. Racial origin of parents known genes of high frequency in certain racial groups (e.g. Ellis-van-Crevald syndrome in the Amish)

7. Parental consanguinity - autosomal recessive disorders

8. Other affected family members with multiple, single gene or chromosomal disorder.

9. Possible maternal uterine abnormalities-deformations

Pregnancy history

1. Maternal drug or alcohol ingestion - teratogenic effects

2. Exposure to radiation (especially therapeutic)- possible mutagenic or teratogenic effects

3. Oligohydramnios - renal agenesis or outflow obstruction with Potter sequence

4. Polyhydramnios- esophageal atresia, neuro-muscular disorders

5. Poor fetal movements -fetal compression, neuro-muscular disorders

6. Breech presentation -neuromuscular disorders

7. Ante natal ultrasound may aid not only in prenatal diagnosis but also holds clues to the diagnosis in the child.

8. Early rupture of membranes - possible fetal compression leading to deformation

Physical examination

1. Whenever an anomaly is noted, it should be described keeping in mind the following directives:

a) Appropriate terminology,[6] b) minor or major anomaly, c) etiology - malformation disruption / deformation and d) time of onset

2. Examination should not be restricted to the patient but should be extended to include all the available family members

3. Whenever feasible, objective criteria should be used in diagnosing anomalies.

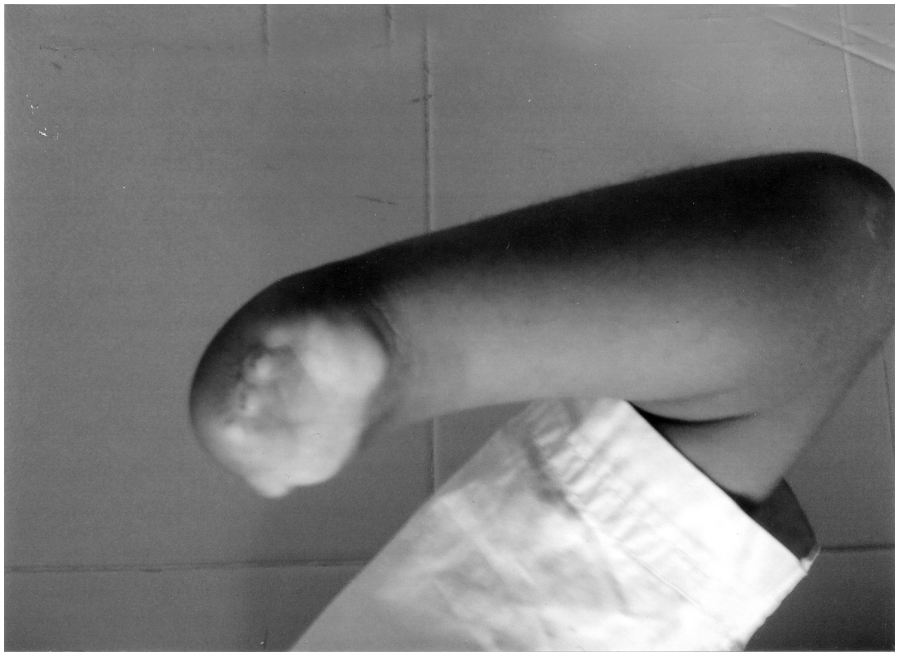

Fig. 1. Amnion rupture sequence, note the amputation and disruption of the finger morphogenesis

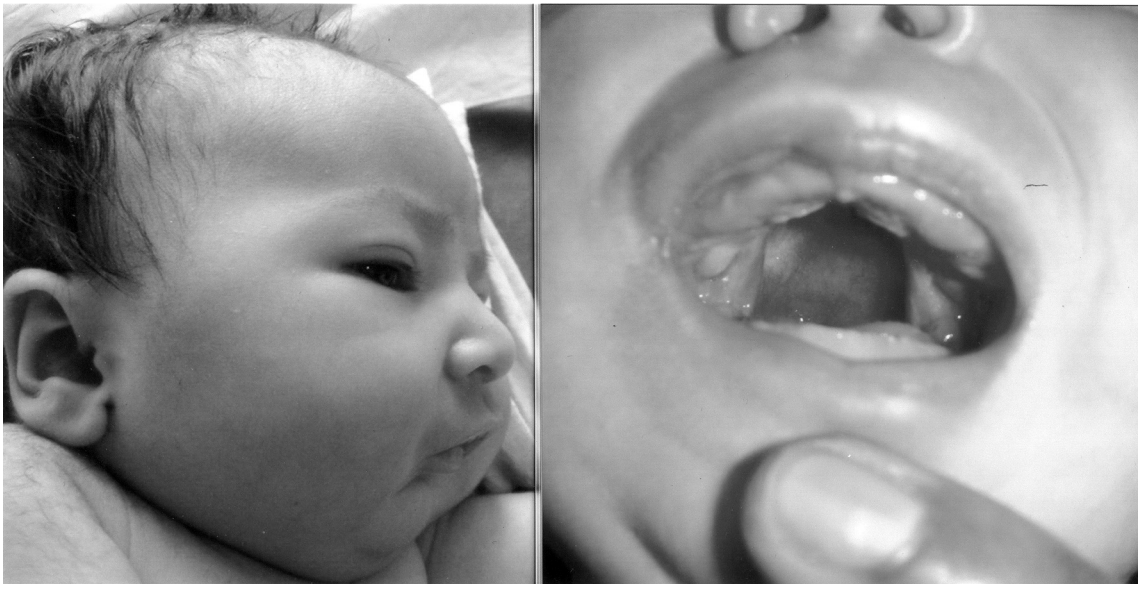

Fig. 2. Pierre robin sequence, note the micrognathia and unusual round shaped palatal cleft unique to this sequence

The reader can refer to various Indian and foreign literature available for anthropometry.[7,8]

4. Consultation should be taken from specialists of other fields in medicine when dealing with a child with multiple anomalies. (Eg. Ophthalmology consultation in Reiger syndrome)

5. Consultation with a specialist in the field of dysmorphology is of utmost importance in the field of dysmorphology for the prompt diagnosis and for further evaluation.

6. The camera plays the role of a stethoscope in the field of dysmorphology. Pictures are not only useful for record purposes and second opinions but also helps in the appraisal of the morphological evolution of a syndrome.

7. Radiography goes hand in hand with physical examination when it comes to anomalies, since they are diagnostic in several conditions such as skeletal dysplasias.

Recognition of genetic syndromes

Some syndromes are so striking to the eye of the pediatrician that a diagnosis is made instantaneously based on the general gist of the patient. This termed as "gestalt diagnosis" is exemplified in the diagnosis of a patient with Down syndrome (Fig.3), wherein multiple minor anomalies make a combination so unique that a diagnosis is rarely missed. In order to have expertise in this mode of "gestalt diagnosis" one has to have a vast experience in seeing similar patients previously in order to create a mental snapshot of the condition. Given the rarity of individual syndromes, such an experience is seldom gained but by a few, hence repeated visual scanning of pictures of various syndromes from authoritative resources will have to suffice.

When immediate recognition is not possible, it is necessary to identify one or more features (handles) which might lead to syndrome diagnosis. Useful handles for the diagnosis are given in Table.2. The best handle or anomaly to be taken to consideration is one which is least likely to be a normal variant. Features like mental retardation, simian crease, clinodactyly are nonspecific and act as poor handles for syndrome delineation. Once a suitable handle is identified, reference should be made to standard monograms on syndromology or computer databases. Table.3 gives the major text and online catalogues of genetic syndromes. When using these databases one should keep in mind, that they are systems for experts and not expert systems.

The Smith's approach to a child with multiple malformations, is a way of classifying syndromes based on the combination of major handles.[5] The author considers this particular approach to be extremely effective and time tested. The following is the major list of classification that is used in the Smith's approach.

- Very small stature, not skeletal dysplasia (eg. Seckel syndrome) (Fig.4)
- Moderate short stature, facial +/- genital (eg. Aarskog syndrome, William syndrome) (Figs.5 and 6)
- Senile like appearance (eg. Werner syndrome) (Fig.7)
- Unusual brain and or neuromuscular findings, with associated defects (eg. Acrocallousal syndrome) (Fig.8)
- Early overgrowth with associated defects (eg. Marshall Smith syndrome) (Fig.9)
- Facial defects as major feature (eg. Frontonasal dysplasia syndrome) (Fig.10)
- Facial-Limb defects as major feature (eg. Hay-Wells syndrome of ectodermal dysplasia) (Fig.11)

Table 2. Useful handles in diagnosis of a syndrome

Head	**Mouth**	**Nails**
Abnormal hair	Cleft lip/palate	Dystrophic
Scalp defects	Absent or abnormal teeth	
Craniosynostosis		
Encephalocele		
Microcephaly		
Eyes	**Limbs**	**Genitalia**
Coloboma	Partial or total absence	Micropenis
Small/absent eyes	Joint webbing	
Cataract	Short limbed dwarf	
Ears	**Digits**	**Skin**
Deafness	Syndactyly	White pathches
Malformed pinna	Polydactyly	Pigmented patches
Preauricular tags	Arachnodactyly	
	Brachydactyly	

Table 3. Major text and online databases of genetic syndromes

Reference texts	**Online and computerized databases**
Smith's recognizable pattern of human malformations	Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim)
Wynne-Davies, Hall and Apley's Atlas of Skeletal Dysplasias	Gene Clinics and GeneTests (www.geneclinics.com)
Gorlin, Cohen and Hennekam - Syndromes of the head and neck.	Winter-Baraitser dysmorphology database (www.lmdatabases.com)
Cassidy and Allanson's management of genetic syndromes	POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations) (www.possum.net)

- Limb defects as major feature (eg. Femoral hypoplasia) (Fig.12)
- Craniosynostosis syndromes (eg. Apert syndrome) (Fig.13)

A special mention is warranted in the case of skeletal dysplasia, since the huge list and the varied presentations of this group of enigmatic conditions is a challenge even to the astute clinician. The following approach based on that

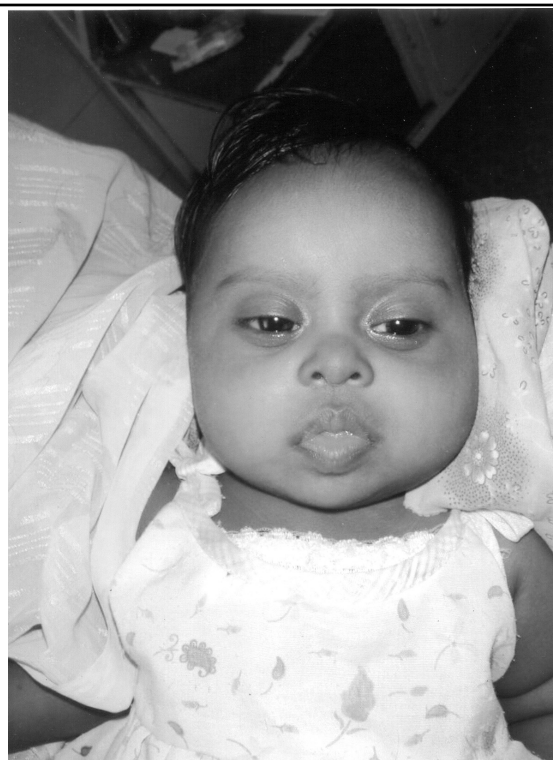

Fig. 3. Down syndrome, note the subtle minor anomalies which help in easy recognition. Features include hypotelorism, upslanting palpebral fissures, low nasal bridge, inner epicanthal folds, protruding tongue and fine hair

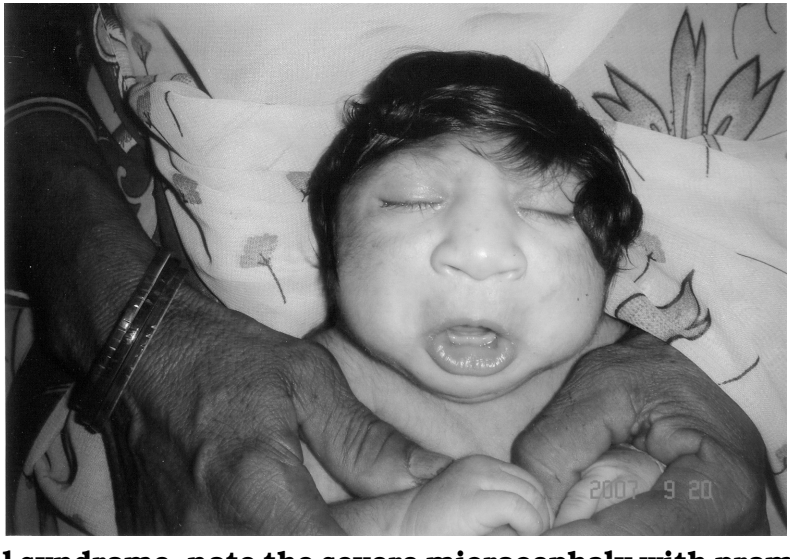

Fig. 4. Seckel syndrome, note the severe microcephaly with prominent nose

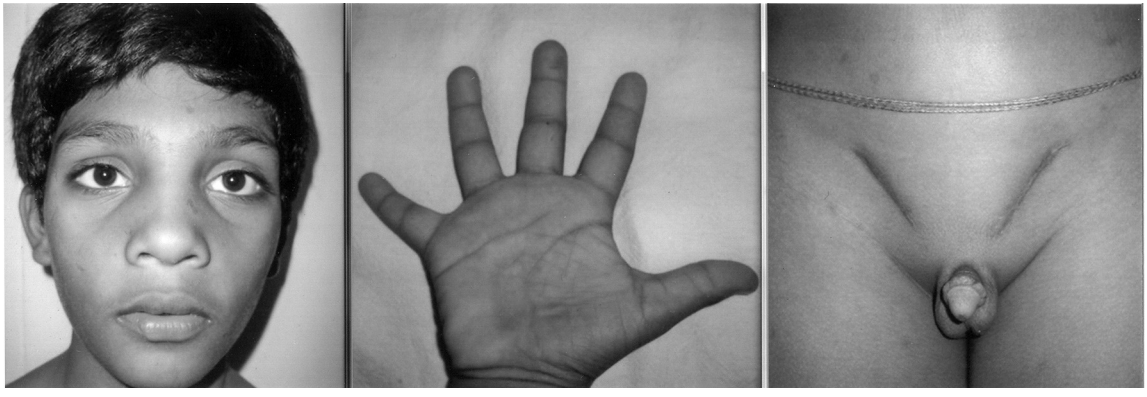

Fig. 5. Aarskorg syndrome, Note the hypertelorism and broad philtrum, hand showing brachydactyly with mild interdigital webbing and characteristic shawl scrotum. Scars due to operation for bilateral inguinal hernia are also seen. Patient was of moderate short stature.

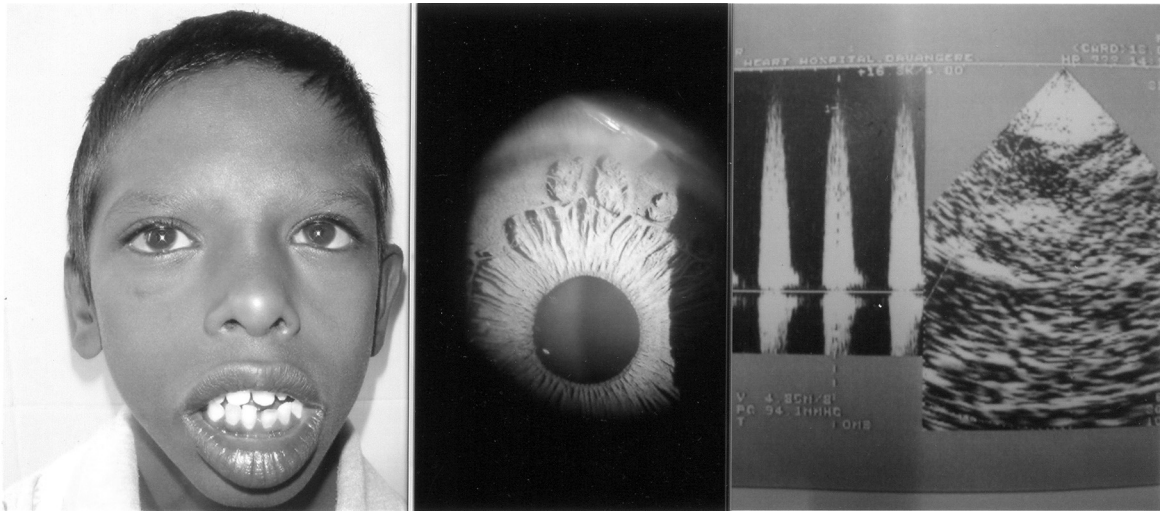

Fig. 6. Williams syndrome, appreciate the periorbital fullness with medial eyebrow flare. Patient has prominent lips with a open mouth. Slit lamp examination revealed characteristic stellate iris pattern. Echocardiogram confirmed the diagnosis of supravalvular aortic stenosis.

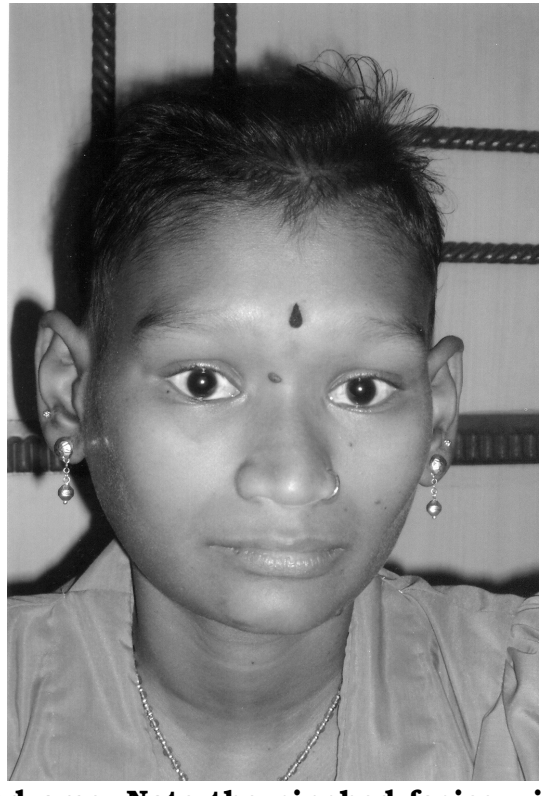

Fig. 7. Werner syndrome, Note the pinched facies with beaked nose and sparse hair, she had hypogonadism

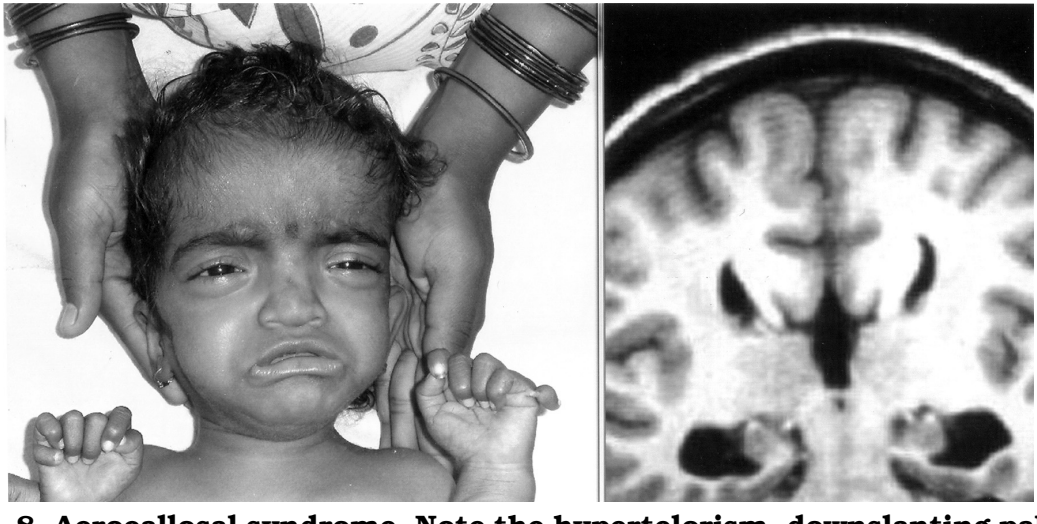

Fig. 8. Acrocallosal syndrome, Note the hypertelorism, downslanting palpebral fissures, broad nasal bridge and short philtrum. Post axial polydactyly is seen in both the upperlimbs. MRI revealed absent corpus callosum.

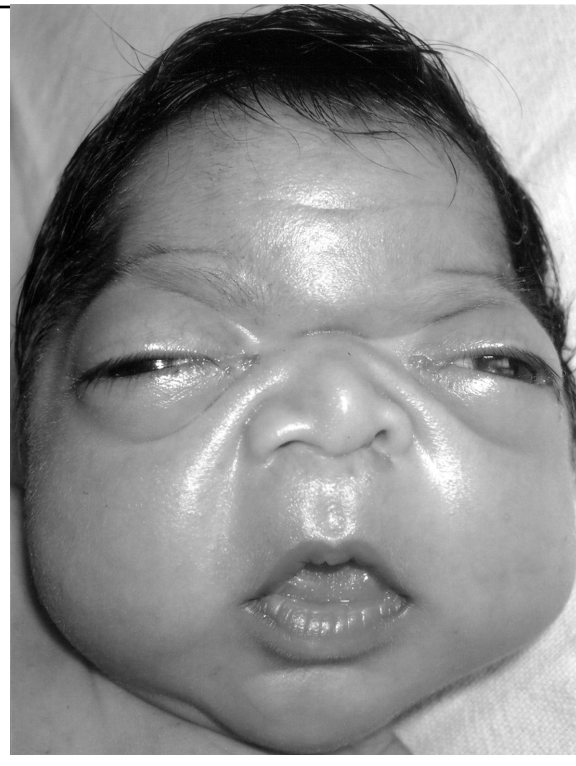

Fig. 9. Marshall-smith syndrome, Appreciate the prominent eyes and forehead with shallow orbit and low nasal bridge.

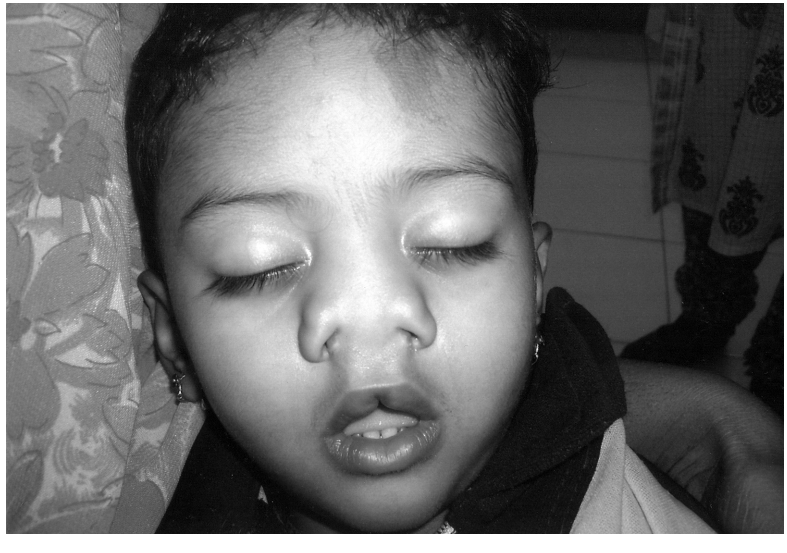

Fig. 10. Frontonasal dysplasia sequence, note the completely divided nostrils with hypoplasia of the prolabium with a median cleft lip.

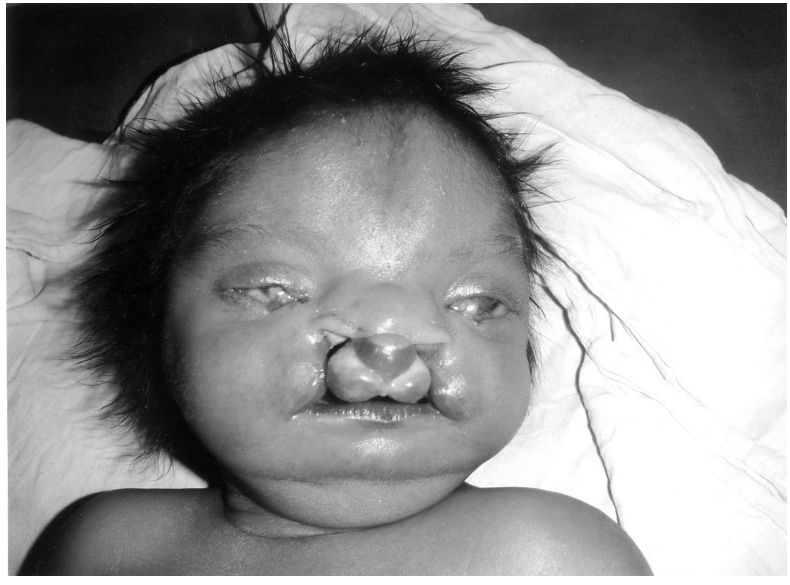

Fig. 11. Hay-Wells syndrome of ectodermal dysplasia, note the obvious ankyloblepharon, broad nasal bridge with bilateral cleft lip and palate. Patient had assoiate dystrophic nails and supernumerary nipples.

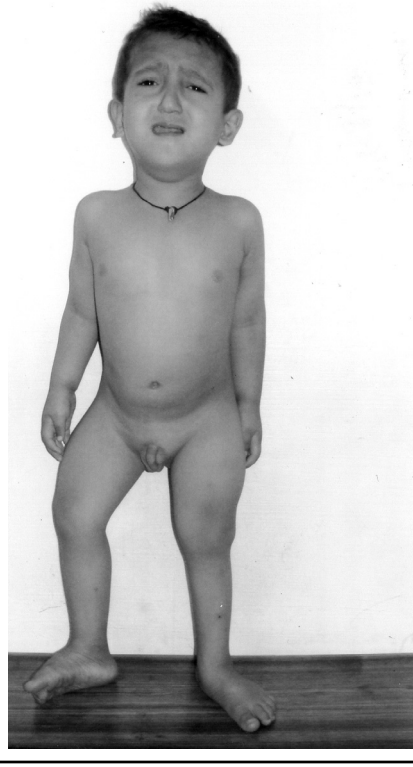

Fig. 12. Femoral hypoplasia-Unusual facies syndrome, note the short lower limbs; face shows upslanting papebral fissures with a short nose and hypoplastic alae nasi. Also note the low set ears. Roentograms revealed bilateral hypoplastic femori.

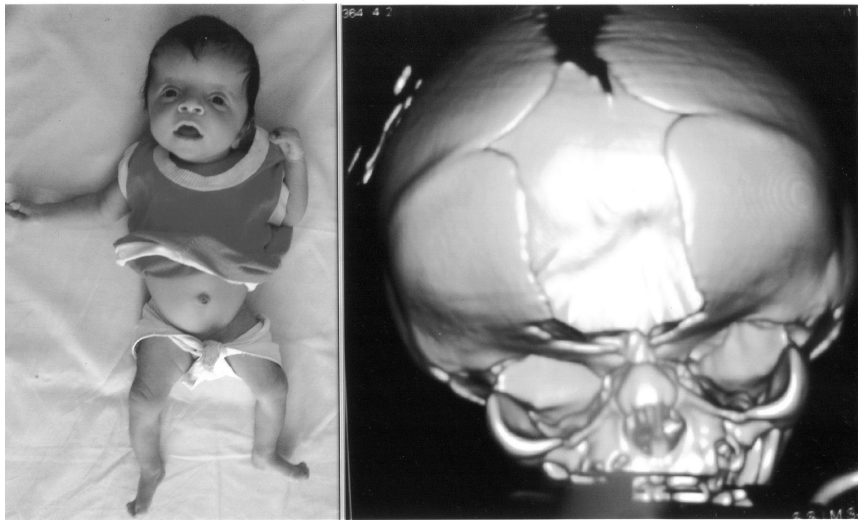

Fig. 13. Apert syndrome the prototype of craniosynostosis syndrome appreciate the high full forehead, hypertelorism and downslanting palpebral fissures. Limbs show varying degress of syndactyly. CT reconstruction of the skull vault shows bilateral coronal suture synostosis.

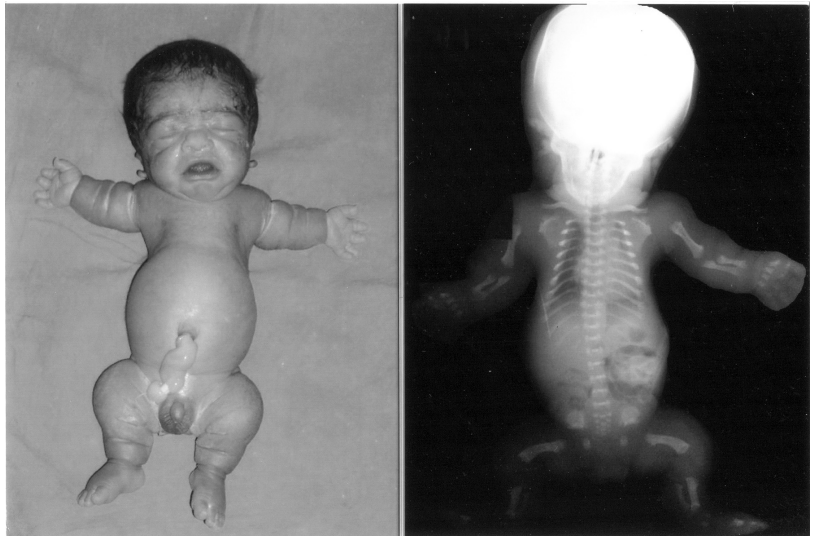

Fig. 14. Thanatophoric dysplasia, note the severe shortening of the limbs which are acromesorhizomelic meaning shortening of the distal, middle and proximal portion of the limbs. Loose folds of skin are also seen in the limbs which are secondary to the shortening. Note the relative macrocephaly with low nasal bridge and narrow thorax. This is a lethal skeletal dysplasia and the baby expired 4 hours after birth secondary to respiratory failure. Note the curved femurs and flat vertebrae on the roentogram.

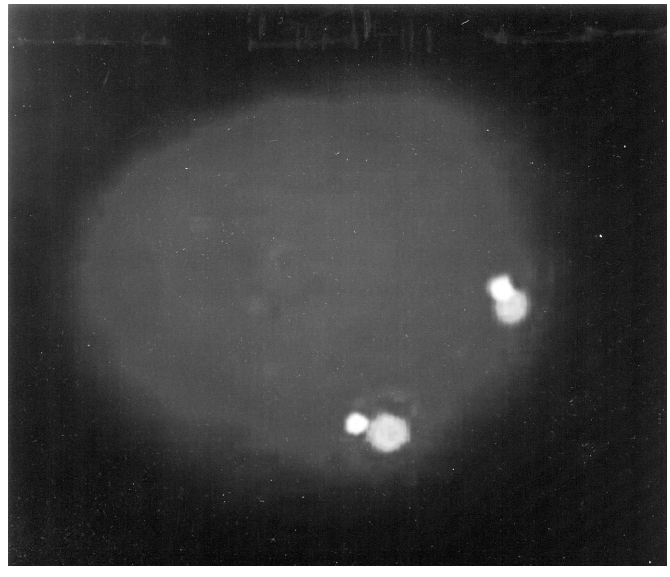

Fig. 15. FISH technique, two red and green signals indicate the presence of a particular region of interest on the four chromatids.

suggested by Bryan.D.Hall is considered to be extremely effective in reaching a diagnosis.[9]

1. Diagnosing short stature
2. Diagnosing disproportionate short stature
3. Diagnosing what causes this disproportion, is it short trunk (eg. spondyloepiphyseal dysplasia) or short limbs (eg. achondroplasia)
4. If short limbed which part of the limbs are affected.
   a) Rhizomelia – proximal shortening i.e. humerus and femur (eg. chondrodysplasia punctata)
   b) Mesomelia – shortening of the middle segment i.e. radius, ulna, tibia and fibula (eg. mesomelic dysplasia)
   c) Acromelia – distal shortening i.e. hand and foot (eg. acromesomelic dysplasia)
   d) Combination – eg. Ellis van crevald syndrome, achondroplasia
5. Diagnosing deformations caused by the osseous abnormalities (eg. craniosynostosis in thanatophoric dysplasia)
6. Diagnosing associated malformation which herald a clue to the actual condition (eg. heart defects in Ellis van crevald syndrome)
7. Categorizing based on the areas involved radiologically: a) epiphysial dysplasias, b) diaphyseal dysplasias, c) metaphyseal dysplasias, d) spine involvement, e) cranial involvement, f) hand involvement
8. Categorizing based on clinical and radiological grounds
   a) Pure skeletal dysplasia (eg. achondroplasia)

b) Malformations associated (eg. Stickler syndrome)

c) Malformation/Mental retardation associated (eg.Campomelic dysplasia)

Laboratory evaluation

Deformations seldom require any laboratory-based diagnostic evaluation, whereas in this post-genomic era genetic testing plays a key role in the evaluation of malformations and associated syndromes.

Karyotyping

Unless a nonchromosomal diagnosis is apparent in a child with multiple malformations it is a useful diagnostic approach to start with a high-resolution karyotype (Chromosome analysis). It is the definitive diagnostic test for aneuploidy syndromes such as Down syndrome, Turner syndrome, etc. Karyotyping also reveals cytogenetic rearrangements such as translocations, duplications and deletions.

Fluorescent In-situ hybridization (FISH)

The FISH technique has revolutionized the field of cytogenetics having tremendous implications in the diagnosis of malformation syndromes. FISH probes by their ability to attach to specific locus on a chromosome bring to light microdeletions that are not visible in the standard karyotype (Fig.15). Table.4 lists the more commonly used and available FISH probes for syndrome delineation.[10]

Upcoming genetic tests

Comparative genomic hybridization combined with microarray technique is a newer addition to the armamentarium of the dysmorphologist. Currently this technique is used mainly for research purposes but will soon be available for the clinical application by pediatrician.

Biochemical testing

Many biochemical genetic defects are associated with dysmorphic features such as mucopolysaccharidosis, Zellweger syndrome and Smith-Lemli-Opitz syndrome. Testing for specific enzyme defect may be diagnostic in these conditions and can be supplemented by finding the underlying genetic defect.

Prenatal diagnosis

In essence it is determination of the status (genetic or otherwise) of the fetus by a variety of techniques (chromosomal, biochemical, DNA, etc.), using a variety of procedures. These include chorionic villus sampling (8-11 weeks), amniocentesis (11-16 weeks), blood analysis by cordocentesis, fetoscopy and embryoscopy. Radiological investigations like antenatal ultrasound, fetal MRI and fetal echocardiogram also assist in prenatal diagnosis of genetic syndromes.

Genetic counselling

Genetic counselling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. The counsellor offers investigations, options and support whereas the "consultand" (the person who seeks the advice) makes his own decision which is known as non-directive counseling. The essential steps include effective diagnosis, risk assessment, proper communication, discussion of options, long term contact and support. Assistance in enrolment of the patient in support groups may be paramount in this era of global communication.

Difficulties

Neonatal period

It is a common occurrence in India, to be faced with a neonate with no antenatal ultrasound

presenting with gross dysmorphic features. This is exemplified in cases such as thanatophoric dysplasia (Fig.14), where early neonatal death is the rule. The attending paediatrician should be able to quickly assess such conditions so as to stop futile resuscitation measures. Neonatal presentation of certain conditions such as Pierre-Robin sequence may be with feeding difficulties or failure to thrive with metabolic encephalopathy in Smith-Lemli-Opitz syndrome or Zellweger syndrome. Adequate expertise is needed for anticipation of difficulties in these conditions.

Evolution of morphology

Some phenotypes evolve with time, such as proteus syndrome and it is the rule in many of the metabolic conditions such as the group of mucopolysaccharidosis and hence a diagnosis is rarely made in the neonatal period. Whereas in certain conditions such as the Beckwith-Wiedemann syndrome, the phenotype tends to dissolve as the age progress. These caveats reinforce the need for proper documentation and photography to study the evolving nature of the condition.

Recent advances

3D Face shape modelling

Human tendency to give objective criteria for subjective intuition has not overlooked the field of dysmorphology. A new modality of three-dimensional (3D) models of facial morphology is showing potential in objective syndrome delineation and discrimination.[11]

Behavioural phenotypes

A well known phenomenon, is the unique behaviour associated with specific syndrome. This is exemplified in the friendly social nature of patients with William syndrome, tendency to overeat in case of Prader-Willi syndrome, self mutilating and destructive behaviour of Lesch-Nyhan syndrome, autistic behaviour in Fragile X syndrome, happy nature of Angelman syndrome and the lovable, friendly and music loving nature of Down syndrome. This old phenomenon termed as the "behavioural phenotype" is gaining more interest, not only as an aid to diagnosis but also in the comprehensive treatment of the patient.

Table 4. Syndromes commonly diagnosed using the FISH technique

Syndrome	Chromsomal abnormality	Clinical features
Angelman syndrome	15q11-q13	MR, spastic gait, happy temperament
Prader-Willi syndrome	15q11-q13	MR, hypotonia, obesity, almond eyes
William syndrome	7q11.2	Aortic stenosis, facial dysmorphism, friendly temperament
Cri-Du-Chat syndrome	5p15.2	MR, cat like cry in infancy, microcephaly
Miller-Dieker syndrome	17p13.3	MR, microcephaly, lissencephaly, furrowing of forehead while crying
Rubenstein-Taybi syndrome	16p13.3	MR, beaked nose, broad thumbs and toes
Velocardiofacial syndrome	22q11.2	Conotruncal heart defects, cleft palate, prominent nose

Points to Remember

- ***Meticulous observation and recording of the deviation from the norms is the cornerstone in dysmorphology.***
- ***Seeing a number of cases and if not possible, visual scanning of photographs and pictures is the key in reaching the correct diagnosis.***
- ***Using objective criteria and appropriate terminology will aid the general pediatrician in effectively diagnosing or grouping a child with multiple congenital defects.***
- ***Cross consultation, expert consultation and database consultation are required to combat the innumerable number of dysmorphic syndromes.***
- ***Lifelong learning – Be a student for ever!***

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GENERAL ARTICLE

INNOCENT MURMURS

**** Anita Khalil***

Abstract: *Cardiac murmurs are a common finding on routine examination in clinical practice. This causes lots of anxiety amongst parents. This article gives an overview to clinically differentiate between pathologiocal and innocent murmur.*

Keywords: *Murmur, Children, Innocent, Cardiac examination.*

Pediatricians often encounter children with heart murmurs, as a part of routine examination in "well baby clinics" or while evaluating for other intercurrent illnesses. The dilemma faced at such a time is to decide which child should be sent for further evaluation or be labelled as an "innocent" murmur.

Murmurs are audible turbulent sound waves in the range of 20-2000 Hz emanating from the heart and circulatory system. The majority of murmurs in pediatric patients are normal or "innocent" occurring in almost 50% of all school going children. Infact 90% of children will have an audible heart murmur at some point in time. The murmur reflects structural heart disease, in infants less than 6 months of age, who are born full term, in contrast to the presence of a murmur in a toddler or an older child.

Cardiovascular examination: Listening to the heart and recognizing normal and abnormal sounds is a skill necessary for health professionals. A detailed history followed by a detailed general and cardiac examination, are particularly pertinent.

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Innocent / Normal murmurs

Innocent heart murmurs arise from cardio vascular structure in the absence of anatomic or physiologic abnormalities.

Characteristics of innocent murmurs

1. These murmurs are ejection systolic or continuous but never diastolic, 2. Intensity – Soft, grade II but never associated with a thrill, 3. S2 – Not affected and the murmur is never accompanied by a mid systolic click, 4.They are accentuated by any hyperdynamic state, (eg) fever, anemia or hyperthyroidism.

Innocent murmurs of childhood are comprised of systolic and continuous types-

1. **Systolic murmurs**

   Vibratory Stills murmur

   Pulmonary flow murmur

   Peripheral pulmonary arterial stenosis murmur

   Supra clavicular systolic murmur

   Aortic systolic murmur

2. **Continuous murmurs**

   Venous hum

   Mammary arterial soufflé

Systolic (Innocent) murmurs

Vibratory Stills murmur

The most commonly heard innocent murmur in childhood is the vibratory systolic murmur described by Still in 1909. The murmur is most typically audible between 2-6 years, is low to medium intensity, confined to early systole, of grade 2-3 and heard maximally at the lower left sternal edge, extending to the apex. The murmur is generally loudest in the supine position and often changes in character, pitch and intensity with upright positioning. The most characteristic feature of the murmur is its vibratory quality, described as "twanging sound, resembling that made by twanging a piece of tense string". The origin of the murmur remains obscure. It may be either due to vibrations of pulmonary valve leaflets during ejection, or physiologic narrowing of left ventricular outflow tract (LVOT) during ventricular contraction or most likely due to the presence of ventricular false tendons.

Pulmonary flow murmur

An innocent pulmonary out flow tract murmur may be heard in thin chested children, adolescents and young adults. The murmur is diamond shaped, early to mid ejection systolic in nature, heard in 2nd to 3rd space at left sternal border. It is a rough murmur of low intensity (grade 2-3) and best heard in supine position and augmented in full expiration. It can be mistaken for an increased pulmonary outflow tract murmur due to atrial septal defect or the murmur of pulmonary valve stenosis.

Peripheral pulmonary arterial stenosis murmur

A common murmur heard frequently in infants and newborns, is due to audible turbulence of peripheral branch pulmonary arterial stenosis, angulation or narrowing. It is an ejection systolic murmur, grade 1-2, low to moderately pitched. It is more apparent in reactive airway disease. Characteristically this murmur is best heard in axilla and back and may be difficult to differentiate from the murmur of peripheral pulmonary artery stenosis of rubella or Williams syndrome.

Supraclavicular / Brachiocephalic systolic murmur

It is a diamond shaped early systolic murmur heard in children and young adults. It is heard in supra clavicular area,best heard in supine position, radiates to the neck and intensity diminishes with extension of shoulder. These murmurs are thought to arise at the origin of brachiocephalic vessel from aorta.

Aortic systolic murmur

This is an ejection systolic murmur heard in aortic area, mostly heard in older children and adolescents. This murmur gets accentuated by fever, anemia and also in athletes with bradycardia. The murmur originates at the left ventricular outflow tract (LVOT), because of obstruction due to increased cardiac output and sometimes it is difficult to differentiate it from hypertrophic cardiomyopathy with LVOT obstruction.

Continuous murmur

Venous hum

The only innocent murmur which is continuous is venous hum. It is audible in the right side of neck adjacent to sternocleidomastoid muscle radiating to infraclavicular area and varying in intensity from grade 1-6. The turbulence at the entry of internal jugular or subclavian vein into the superior vena cava may be the origin of the murmur.

Mammary artery soufflé

This is a murmur which is recognized in late pregnancy and lactation, occasionally in

adolescence, and its origin is from the enlarged vessels of the chest wall. It has to be differentiated from patent ductus arteriosus and A-V fistula.

Points to Remember

- ***Clinical examination of a patient is the best way to correctly diagnose and classify a murmur by careful auscultation. Routine echocardiography also may not be necessary.***
- ***Decision to refer a child for further evaluation of a murmur, whether it is innocent or pathological depends on the clinical impression and also on the competence of the examining pediatrician. Anxiety levels of the parents and also whether the child is available for further follow up are other factors to be considered for referral and or echocardiography.***

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CLIPPINGS

Martin H. Osmond,Terry P. Klassen, George A. Wells, Rhonda Correll, et al. CATCH: a clinical decision rule for the use of computed tomography in children with minor head injury. CMAJ 9th March, 2010.

There is controversy about which children with minor head injury need to undergo computed tomography (CT). This study aims to develop a highly sensitive clinical decision rule for the use of CT in children with minor head injury. Consecutive children with blunt head trauma presenting with a score of 13–15 on the Glasgow Coma Scale and loss of consciousness, amnesia, disorientation, persistent vomiting or irritability were enrolled for the study. The authors derived a decision rule for CT of the head consisting of four high-risk factors (failure to reach score of 15 on the Glasgow coma scale within two hours, suspicion of open skull fracture, worsening headache and irritability) and three additional medium-risk factors (large, boggy hematoma of the scalp; signs of basal skull fracture; dangerous mechanism of injury). The high-risk factors were 100.0% sensitive (95% CI 86.2%–100.0%) for predicting the need for neurologic intervention and the medium-risk factors resulted in 98.1% sensitivity (95% CI 94.6%–99.4%) for the prediction of brain injury by CT and would require that 52.0% of patients undergo CT.

Interpretation: The decision rule developed in this study identifies children at two levels of risk. Once the decision rule has been prospectively validated, it has the potential to standardize and improve the use of CT for children with minor head injury

GENERAL ARTICLE

ADVANCES IN THE ANTIMICROBIAL THERAPY OF NOSOCOMIAL INFECTIONS

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Abstract: *Nosocomial Infection (NI) is among the most difficult problems confronting clinicians who deal with severely ill children. NIs occur world wide and affect both developed and developing countries. Many factors promote infection among hospitalized patients such as decreased immunity among the patients, variety of medical procedures, invasive techniques, health care personnel, etc. These factors are potential routes of infection and the transmission of drug resistant bacteria among crowded hospitals where poor infection control practices may facilitate transmission. New antimicrobial agents with unique mechanisms or improved antimicrobial activity compared with agents in the same class are needed to treat resistant pathogens as they become more prevalent among hospitalized patients. Recently some new antimicrobials are launched in the market and made available to healthcare providers for use in the patients. Several new agents are currently in the pipeline and some of them may be available in the future for use in the clinical practice. The detail of these agents with reference to their clinical utility is discussed.*

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Keywords: *Nosocomial infections, Recently launched antimicrobials, Antimicrobials in the pipeline.*

The term nosocomial infection is derived from Greek word 'nosocomeion' meaning hospital, thereby nosocomial infection means hospital infection or hospital acquired infection.[1]

A nosocomial infection (NI) is defined as an infection that was neither present nor incubating at the time of hospitalization and that develops 48 or more hours after hospital admission or within 10 days of discharge from the hospital.[2] It is associated with high morbidity and mortality. NI is among the most difficult problems confronting clinicians who deal with severely ill children. It also adds significantly to the economic burden. Many factors promote infection among hospitalized patients such as decreased immunity among the patients, variety of medical procedures, invasive techniques, etc. These factors are potential routes of infection and the transmission of drug resistant bacteria among crowded hospitals where poor infection control practices may facilitate transmission. New antimicrobial agents with unique mechanisms or improved antimicrobial activity compared with agents in the same class are needed to treat resistant pathogens as they become more prevalent among hospitalized patients.

Frequency of nosocomial infection

NIs occur world wide and affect both developed and developing countries. A prevalence survey conducted under the auspices of WHO in 55 hospitals of 14 countries representing four WHO Regions (Europe,

Eastern Mediterranean, South East Asia and Western Pacific) showed an average of 8.7% of hospital patients had NIs. At any time, over 1.4 million patients world wide suffer from infectious complications acquired in the hospital. The highest frequencies of NIs were from hospitals in the Eastern Mediterranean and South East Asia regions, 11.8 and 10% respectively.[3]

Host factors

Children are more vulnerable to infections due to incomplete maturity of immune system and congenital abnormalities. Immune deficiency is the major factor in preterm babies who are hospitalized for prolonged time and exposed to invasive monitoring and therapeutic procedures. Rates of NIs as high as 7 to 25% are reported in NICUs.[2] Infants with congenital anomalies have a high risk of NIs because they need prolonged hospitalization, multiple operations and have extended exposure to invasive monitoring and supportive equipments. Children with chronic diseases such as diabetes mellitus, renal failure, acquired immuno deficiency syndrome (AIDS) and malignancies have an increased susceptibility to infections with opportunistic pathogens.[3,4]

Sources of microbes

Common sources of NIs in infants and children include health care personnel, invasive monitoring, supportive equipments, blood products, infant formula, expressed human milk, etc. Procedures like fetal monitoring with devices, fetal transfusion, umbilical cannulation are other risk factors for NIs. Contaminated solutions used for parenteral nutrition may be responsible for sporadic and epidemic infections in the nursery.[2,4]

Environmental factors

Health care settings are an environment where both infected persons and persons at increased risk of infection congregate. Patients with infections or carriers of pathogenic microorganisms admitted to hospital are potential sources of infection for patients and staff. Patients who become infected in the hospital are a further source of infection. Neonatal nurseries, burns units and intensive care units which are usually crowded contribute to the development of NIs.[3]

Microbial agents

The patient is exposed to a variety of microbes during hospitalization. Factors influencing the nature and frequency of NI include virulence of the organism, inoculum of infected material, resistance of the organisms, etc. Many different bacteria, viruses, fungi and parasites may cause NIs.

Most infections acquired in the hospital today are caused by microorganisms which are common in the general population in whom they cause no or milder disease than among hospital patients. These organisms are Staph.aureus, coagulase negative staphylococci, enterococci, Enterobacteriaceae etc.[3]

Nosocomial infection sites[3]

The most common sites for nosocomial infections are,

- Urinary tract
- Lower respiratory tract (mainly pneumonia)
- Surgical site
- Blood
- Gastrointestinal tract

Skin and soft tissue infections, sinusitis, conjunctivitis etc., are other NIs.

Urinary tract infections (UTI)

The most frequently used indwelling catheter is the urinary catheter in the bladder.

The rates of infections are directly proportionate to the duration of catheterisation. Protocols for catheter care are useful in reducing infections.[4,5] Instrumentation of urethra and bladder is another cause for nosocomial UTIs. E.coli SPC remains the most common infecting organism, but a wide variety of other organisms may be isolated such as klebsiella, enterococcus, Staph.epidermidis, Pseudomonas aeruginosa, Candida albicans, etc.[6]

UTI usually follows formation of biofilm on the internal and external surfaces of the catheter. The biofilm protects organisms from antimicrobials as well as host immune response. Asymptomatic catheter acquired UTI should not be treated with antimicrobials. Symptomatic UTI should be treated with appropriate antimicrobials. Whenever possible antimicrobial selection should be delayed until culture results are available. The duration of therapy is usually 10 to 14 days.[3,4]

Nosocomial pneumonia

Normal children frequently aspirate oropharyngeal secretions during sleep but they do not develop pneumonia because of competent host defense mechanism and probably less virulent organisms. The source of organisms for nosocomial pneumonia may be endogenous (aspiration) or exogenous (inhalation). Nasotracheal intubation (42% vs 6% oral) and prolonged nasogastric tubes in situ may contribute to poor drainage resulting in infections.[3,4,7]

The choice of antibiotics for nosocomial pneumonia is difficult due to two factors, the hospital acquired pneumonias are likely due to highly resistant organisms as most of the patients in PICU are treated with multiple antibiotics and multiple organisms are responsible for pneumonia. Multiple organisms are very often cultured from respiratory secretions of these patients. Because of the emergence of multi drug resistant extended spectrum beta lactamase (ESBL) producing gram negative organisms and the increasing role played by MRSA even a protocol combining ceftazidime or imipenem and amikacin might not ensure adequate coverage.[4]

Blood stream infections

The use of short or long term indwelling catheters is no longer restricted to intensive care units as oncologists and surgeons often treat or even discharge children with indwelling lines. Central venous catheter (CVS) related infections include exit, tunnel, pocket and catheter related blood stream infections.

Etiologic agents for catheter related infections include coagulase negative staphylococci, enterococci, staphylococcus aureus, pseudomonas, fungi, etc. These may vary with each institution.[3-8]

CSF shunt infections

The most common causative organism is coagulase negative staphylococci, as contamination is invariably at the time of shunt insertion. Other pathogens include s.aureus, pseudomonas aeruginosa, etc. Every effort at identification of causative organism is a must prior to starting antimicrobials of any nature. CSF from a lumbar tap and from the ventricles must be separately sampled and shunt tubes sent for culture once it is removed.[4]

Surgical site infections

Surgical site infections are also frequent. The infection is usually acquired during the surgery, either exogenously (e.g. from the air, medical equipments, surgeons and other staff) or endogenously from the flora on the skin or in the operative site or rarely from blood used during surgery. S. aureus, E.coli, Proteus, enterococci, staph.epidermidis are common pathogens responsible for these infections.[2-5,7]

Skin and soft tissue infections

Ulcers, burns and bedsores encourage bacterial colonization and may lead to systemic infection.[3,8] Sinusitis without pneumonia can be a cause of fever in the PICU. In children, this possibility is often ignored.[9]

Gastroenteritis

This is common nosocomial infection in children, where rota virus is a chief pathogen.[4] Salmonella, shigella are other organisms responsible for nosocomial GI tract infections.[4,5]

Management of nosocomial infections

Many antimicrobial agents are available today and antibiotic therapy should theoretically be chosen after isolation of the organism and its susceptibilities have been established. More frequently and particularly in the intensive care units, the antibiotic therapy is empirical because of emergency situations, severity of infections in immunocompromised, neutropenic and newborn patients. To offer the optimal therapy to treat these difficult infections efficiently, the local microbiological flora and their current resistance pattern should be taken into account.[2,10]

The choice of empiric antibiotic therapy for the treatment of any NI before microbiology is available requires,

- Surveillance data on a regular basis of predominant organisms in the hospital and intensive care units.
- Surveillance of the current resistance patterns of these microorganisms.
- Identification of out breaks on NI involving one or more prevalent organisms.[10]

Principles of empiric therapy[2,4,5,10,11,12]

The conventional empiric therapy should be broad spectrum to ensure coverage of most of the suspected pathogens. Combination therapy with an anti pseudomonal penicillin (piperacillin) plus an aminoglycoside or an antipseudomonal cephalosporin (ceftazidipme) plus an aminoglycoside have been for long the initial regimen recommended. However, in situations suggestive of gram positive organisms such as MRSA, the addition of a glycopeptide forms part of empiric therapy.

During outbreaks of NI with high probability of cross contamination of a previously identified endemic multiresistant organism such as pseudomonas aeruginosa, carbapenem (imipenem or meropenem) along with either an aminoglycoside (amikacin) or a fluoroquinolone (ciprofloxacin) should be considered.

Any empiric therapy should be reassessed 2 or 3 days after its initiation. Modifications should be made on the basis of report of antibiotic sensitivity tests available on day 2 or 3 and clinical response of the patient. Potential choice of more suitable combination therapy or to switch over less expensive, less toxic antibiotics is recommended when the clinical status of the patient permits.

When anaerobic bacteria are suspected for instance in surgical abdominal polymicrobial infection or in aspiration pneumonia, the addition of clindamycin or cefoxitin or metronidazole is recommended. Imipenem is a useful alternative for mixed aerobic and anaerobic infections.

If legionellosis is suspected as in a case of atypical pneumonia, erythromycin and rifampicin either alone or in combination are the antibiotics of choice.

In patients of neutropenia with neutrophil count less than 500/cu.mm and fever 38.3^{o}C, ceftazidime plus vancomycin is recommended as initial antibiotic therapy. If MRSA or other gram positive resistant organisms are not

Table 1. Therapeutic strategies for documented nosocomial infections

	Monotherapy	Conventional combinations	Alternatives
Gram-negative organisms			
Escheric hia coli	Ceftazidime or aztreonam or cefpirome/cefepime: amoxicillin-clavulanic acid: fluoroquinolone (in UTI)	Cefotaxime + amikacin: piperacillin + tazobactam:+ cefoxitin or aztreonam + aminoglycoside	Imipenem alone Imipenem aminoglycoside imipenem + fluoroquinolone
Klebsiella spp: SBL -	Ceftazidime or : cefoperazone or cefepime/cefpirome amoxicillin-clavulanic acid	Piperacillin + tazobactam: ticarcillin + clavulanic acid: cefotaxime + aminoglycoside	Imipenem alone Imipenem + aminoglycoside: imipenem + fluoroquinolone
ESBL+	Imipenem or cefepime : fluoroquinolone (in UT)	Imipenem + aminoglycoside: piperacillin + tazobactam + amikacin	Imipenem + ciprofloxacin
Enterobacter spp.	Imipenem or meropenem: cefpirome/cefepime: piperacillin + tazobactam	Third generation cephalosporin + aminoglycoside: aztreonam + amikacin	Imipenem + fluoroquinolone: aminoglycoside + ciprofloxacin
Pseudomonas aeruginosa	Penicillins (ticarcillin, piperacillin, azlocillin) Cephalosporins . (ceftazidime, cefpirome/cefepime) Imipenem. meropenem	Ticarcillin aztreonam or ceftazidime + sulbactam + tobramycin or amikacin: ceftazidime + fluoroquinolone	Antipseudomonal penicillin + fluoroquinolone: aztreonam + amikacin: aminoglycoside + ciprofloxacins fosfomycin + ciprofloxacin
Gram-Positive organisms			
Staphylococcus aureus: MSSA (methicillin-susceptible)	Penicillins, cloxacillin: cefazolin cefalothin: Second generation cephalosporin: cefotaxime aminoglycosides	Penicillin + aminoglycoside (oxacillin + gentamicin): tetracycline + aminoglycoside: amoxicillin + clavulanic acid: ampicillin + sulbactam	Fluoroquinolone + fusidic acid: fosfomycin + L-lactam: + fusidic acid + cloxacillin
MRSA (methicillin-resistant)	Vancomycin: imipenem-cilastatin: meropenem: fusidic acid	Rifampicin + vancomycin: fusidic acid + glycopeptide: fosfomycin + aminoglycoside: vancomycin + fluoroquinolone	Imipenem + vancomycin: fusidic acid + fosfomycin: fusidic acid + glycopeptide: fusidic acid + rifampicin:
Coagulase-negative staphylococci	Same indications as for MRSA, with higher resistance rates to : quinolones, aminoglycosides, clindamycin, cotrimoxazole.		Imipenem + fosfomycin: aminoglycoside
Enterococcus spp.	Ampicillin: imipenem: piperacillin: glycopeptide (in nosocomial UTI only)	Ampicillin + gentamicin: vancomycin + aminoglycoside	Teicoplanin + penicillin: imipenem + glycopeptides: piperacillin + teicoplanin

suspected monotherapy with ceftazidime, cefepime or meropenem may be given.

Therapeutic strategies for documented nosocomial infections[10] (Table-1)

The identification of aetiological agents involved in a given outbreak of NI should rely on an efficient clinical microbiology, laboratory and good epidemiology practices within the hospital wards. Moreover, the choice of single agent or a combination based on clinical consideration should also refer to the known pattern of susceptibility and resistance.

The patient's condition, severity of underlying disease, the presence of various devices like catheters, prosthesis, ventilatory equipment, etc. are important factors which may modify the choice of antibiotics.

The site of NI and pharmacokinetic consideration are other points leading to an appropriate choice of antibiotics. Adequate delivery of drug in infected tissues depends on dosage and route of administration. Penetration of drug into CSF, variable penetration of drugs into cells (macrophages) to reach and kill the intracellular organisms (legionella pneumophila) are noteworthy considerations before choosing the antimicrobials.

Antimicrobials in specific nosocomial infections

Nosocomial pneumonia

Nosocomial pneumonia is one of the common nosocomial infections associated with substantial morbidity and mortality. The common causative agents are Pseudomonas aeruginosa, K.pneumoniae, S.pneumoniae, H.influenzae, E.coli, M.catarrhalis and Staph.aureus. The lung parenchyma and bronchial tissues are generally accessible to penicillins, third generation cephalosporins and fluoroquinolones at concentrations high enough to inhibit most organisms. However, the multiple mechanisms of resistance exhibited by two major pathogenic organisms, pseudomonas aeruginosa and s.aureus impose the use of combination of synergistic antibiotics, beta lactam and aminoglycoside. A specific problem is S.aureus strains with reduced vancomycin susceptibility. This leads to increased use of newer compounds such as quinupristin and dalfopristin.

Although less frequently isolated from nosocomial pneumonia, S.pneumoniae has become a world wide problem (except India at present) because of its increasing resistance to penicillin and most beta lactam antibiotics. It can be overcome by higher dose of penicillin or with third generation cephalosporin (Ceftriaxone) or fourth generation cephalosporins like cefepime and cefpirome.[2,4,10]

Ribavirin in treatment of RSV infection is indicated in patients with underlying immunodeficiency, chronic lung disease, congenital heart disease, preterm infants etc.[2]

Amphotericin B is the treatment of choice for invasive nosocomial respiratory infections caused by fungi including aspergillosis and candidiasis. Itraconazole and fluconazole have been used successfully instead of amphotericin B in such conditions.[2]

Nosocomial blood stream infection

There are several sources of bacteremic extension, mainly nosocomial pneumonia and UTI. Skin and soft tissue infections (particularly infected burn and bed sores) and surgical wounds are other sources of bacteremia. Gram positive organisms, MRSA and coagulase negative staphylococci are common organisms in this situation. Combinations of imipenem plus fosfomycin or vancomycin or an aminoglycoside seem to offer potential efficacy.[2,4,5,10]

Skin and soft tissue infections

Topical wound care using various agents like 0.5% Silvernitrcite solution, 10% mafenide acetate cream and silver sulfadiazine, local antibiotics and prophylactic systemic antibiotic therapy constitute the best approach to prevent burn wound and bed sore infections.[10]

Recently launched antimicrobials

New antimicrobial agents with unique mechanisms of action or improved antimicrobial activity compared with molecules in the same class are needed to treat resistant pathogens as they become more prevalent among hospitalized patients causing nosocomial infections. Unfortunately, most big pharmaceutical companies have reduced or even ceased efforts to discover new antimicrobial agents, primarily for financial reasons. Still some new agents have become available for healthcare providers since 2000, the most important are linezolid, quinupristin – dalfopristin, daptomycin, tigecycline, colistin, caspofungin, variconafne, etc.

Linezolid

Linezolid is the first of a new class of antimicrobial agents, the oxazolidine. It was approved by US FDA in 2000 for the treatment of skin and soft tissue infections, lower respiratory tract infections due to susceptible organisms and vancomycin resistant enterococcus faecium infections including cases with concurrent bacteremia.[13]

Chemistry: The oxazolidines are unique because they are totally synthetic. Therefore, there are no pre-existing specific resistance genes among gram positive bacteria against this group of drugs. Their mechanisms of action is also unique, which decreases the possibility of cross-resistance with currently available agents. They were originally developed as monoamine oxidase inhibitors for treatment of depression, but subsequently discovered to have antimicrobial activity. The first oxazolidine antimicrobial agents were developed in the late 1970s for the control of bacterial and fungal foliage diseases of various plants. A series of chemical modifications of oxazolidine nucleus led to the discovery of two agents, eperezolid and linezolid. Although both agents showed excellent in vitro activity against gram positive bacteria, linezolid was chosen for further clinical development.[13,14,15,16]

Mechanism of action and resistance: The oxazolidines are considered bacteriostatic. They have a unique mechanism of action that interferes with the first step of bacterial ribosomes assembly. They bind to site on the 50 S ribosomal subunit near its interface with the 30 S unit, thus preventing the formation of 70 S initiation complex. No other known antimicrobial agent inhibits this process, therefore, there is no cross-resistance. Being a synthetic compound, naturally occurring resistance is unlikely.

Spectrum of activity[13]

The oxazolidines have excellent in vitro activity against the major gram positive bacteria and some gram negative bacteria. More than 90% of gram positive bacteria are inhibited by linezolid such as staph.aureus, listeria monocytogenes, staph.epidermidis, s.pneumoniae, beta hemolytic stretptocci, s.viridans, etc. There are not enough data on linezolid effectiveness against atypical organisms including legionella pneumophila, mycoplasma pneumoniae, chlamydia pneumoniae, etc.[13-16]

Pharmacokinetics: Linezolid is 100% available, when given orally or intravenously. Maximum plasma concentrations are achieved 1 to 2 hours after an oral dose. Dosage alteration is not recommended with renal or hepatic insufficiency.[13]

Indications: The US FDA has approved linezolid for the treatment of Vancomycin – resistant Enterococcus faecium infections, pneumonia by streptococcus pneumoniae or staph.aureus, complicated skin and soft tissue infections caused by S. aureus, S. pyogenes, etc. No comparative trials of linezolid in patients with endocarditis, osteomyelitis and meningitis have been performed.[13-16]

Adverse effects: Myelosuppression was noted in animal studies and therefore it is recommended to monitor complete blood count weekly in patients who receive linezolid for more than two weeks and those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression and those with chronic infections.[13]

Dosage: In children the dosage recommended is 20 to 30 mg/kg/day, orally or intravenously 8 hourly or 12 hourly.

Quinupristin - Dalfopristin

Quinupristin – Dalfopristin is a combination of streptogramins that was first approved by the US FDA in September 1999 for use in the treatment of serious or life-threatening infections associated with vancomycin resistant Enterococcus faecium bacteremia and complicated skin and soft tissue infections caused by MSSA and streptococcus pyogenes.

Chemistry: The streptogramins belongs to the macrolide – lincosamide streptogramins group of antibiotics. They are macromolecular antibiotics produced by streptomyces pristinaepiralis. Quinupristin – dalfopristin is made up of chemically modified, water-soluble injectable derivatives of type-B streptogramin (quinupristin) and type-A streptogramin (dalfopristin) in a 30 : 70 ratio.[13]

Mechanism of action and spectrum of activity: This combination of quinupristin dalfopristin is synergistic and is bactericidal. The main target is the bacterial 50 S ribosome that results in inhibition of protein synthesis. The antimicrobial activity of quinupristin – dalfopristin was evaluated and demonstrated in vitro activity against 90% of strains of a wide variety of multi drug resistant gram positive organisms including E.faecium, MSSA, MRSA and staph. epidermidis. However, strains of Enterococcus faecalis were generally resistant to it. Similarly, aerobic gram negative enteric bacilli were not susceptible to quinupristin, dalfopristin. It has also demonstrated in vitro activity against S.pneumoniae, H.influenzae, Legionella species, Mycoplasma and Chlamydia pneumoniae.

Indications: The indications for treatment are bacteremia with unknown focus, bone and joint infection, catheter related bacteremia, intraabdominal infection, UTI and skin and soft tissue infections.[10,13]

Adverse reactions: The most common adverse effects are pain and inflammation at the infusion site. Other side effects include arthralgia, myalgias, nausea, vomiting, diarrhoea, headache, rash and pruritus.

Dosage: The recommended dosage of quinupristin – dalfopristin for the treatment of vancomycin resistant E.faecium infections in adults is 7.5 mg per kg intravenously every eight hours. The dose for skin and skin structure infections is 7.5 mg per kg given intravenously every 12 hours. The duration of treatment for vancomycin resistant E.faecium infections should be based on the site and severity of the infection. The recommended minimum duration of treatment for complicated skin and skin structure infections is 7 days. The dosage of quinupristin – dalfopristin does not have to be adjusted in patients with renal impairment. Pediatric dosing is currently not available.

Daptomycin

Daptomycin is the first agent of a new class of antibiotics called cyclic lipopeptides drug. It was approved by the US FDA in 2003 for use in adults in the treatment of skin and soft tissue infections and lower respiratory tract infections due to susceptible organisms.[13]

Mechanism of action: It binds to bacterial membranes and causes rapid depolarization of membrane potential. This results in inhibition of protein, DNA and RNA synthesis resulting in bacterial cell death.[13,17]

Spectrum of activity: Daptomycin has shown excellent in vitro activity against s.aureus, (MSSA & MRSA), Streptococcus pyogenes, Enterococcus faecalis, Clostridium difficile etc.[13,17]

Indications: Daptomycin has shown clinical efficacy in skin and soft tissue infections. Clinical studies are going on for bacterial endocarditis, bacteremia and osteomyelitis.[13,17]

Adverse reactions: The most commonly reported side effect of daptomycin is elevation of CPK. Therefore, it is recommended that patients be monitored for muscle pain, weakness and weekly CPK levels while on therapy. Another rare but serious side effect is neuropathy. Gastrointestinal, injection site reactions and headache are other side effects.[13,17]

Dosage: The dosage of daptomycin is 4 mg/kg iv once daily for 7 to 14 days. Pediatric dosing is currently not available.[13]

Tigecycline

Tigecycline is a new, semisynthetic glycycycline, approved by the US FDA for the treatment of skin and soft tissue and intra abdominal infections.[13]

Mechanism of action: Tigecycline is bacteriostatic and acts by binding to the bacterial 30S ribosomal subunit that leads to inhibition of protein synthesis.

Spectrum of activity: Tigecycline is highly effective against most gram positive organisms including Staph.aureus, coagulase negative staphylococci, enterococcus species, Streptococcus pneumoniae, group A streptococci, group B streptococci, viridans streptococci etc. It also has good activity against E.coli, klebsiella, proteus, salmonella, citrobacter species, etc. It has also shown some activity against atypical organisms.[13,18]

Indications: Tigecycline is at present approved for the treatment of skin and soft tissue and intraabdominal infections.

Adverse reactions: The most common side effects of tigecycline are nausea and vomiting. Other side effects include pain at the injection site, swelling and irritation.[13,18]

Dosage: Tigecycline is administered by intravenous infusion over 30 to 60 minutes. The initial dose is 100mg followed by 50 mg every 12 hours. The usual duration of treatment is 5 to 14 days. Pediatric dosing is currently not available.[13,18]

Colistin

Colistin, also called polymyxin E, belongs to the polymyxin group of antibiotics. It was first isolated in Japan in 1949 from Bacillus Polymyxa var. Colistinus and became available for clinical use in 1959. Colistin was given as intramuscular injection for the treatment of gram negative infections. But due to its significant side effects and availability of aminoglycoside, its parenteral use was stopped. It was later used as topical therapy and is still used in aerosol form for patients with cystic fibrosis.[19,20] More recently,

a number of centres around the world have used colistin intravenously for otherwise pan resistant nosocomial infections, especially those due to pseudomonas and acenatobacter species.[19,20]

Two different forms of colistin are available commercially, colistin sulfate (Colistin) and sodium colistin methanesulfonate (CMS). Colistin is primarily used topically, whereas CMS is used parenterally and both forms may be given by inhalation.

Colistin remains active in vitro against almost all strains of P.aeruginosa, Klebsiella, pneumoniae, Acetobacter spp and Enterobacter spp. Cross resistance with other antibiotics has not been reported and acquired resistance is rare. Its response has been found better in patients with blood stream infections resulting from urinary tract infection. It was less effective in patients with osteomyelitis, biliary tract infections, endocarditis etc. It was ineffective in the treatment of gram negative infections in neutropenic patients.[19,20]

Colistin is polycationic and has both hydrophilic and lipophilic moieties. These interact with the bacterial cytoplasmic membrane, changing its permeability. This effect is bactericidal.

The following preparations are available for use in the practice.

- Colomycin 5,00,000 units is 40 mg colistimethate
- Coly-Mycin M 150 mg 'colistin base' is 400 mg colistimethate or 5,00,000 units.

There is no standardized dosing of colistin and no detailed trials of pharmacology available. Colomycin has a recommended dose of 1 to 2 million units thrice daily for patients weighing 60 kg or more with normal renal functions. Coly-Mycin has a recommended dose of 2.5 to 5 mg/kg colistin base a day. Each country has different generic preparation of colistin and recommended dose will depend on manufacturer. The complete absence of any regulation or standardization of dose makes intravenous colistin dosing a nightmare for any physician.

Colistimethate aerosol is used to treat pulmonary infections, especially in cystic fibrosis. In the UK and Australia, the dose most commonly used is 40 mg (1 million units) nebulized colistimethate thrice daily.[19,20]

Adverse effects: The main toxicities are nephrotoxicity and neurotoxicity, but this may reflect very high doses given, which are much higher than the doses currently recommended.[19,20]

Caspofungin

Caspofungin is the first antifungal agent from a new class of drugs. It is a semisynthetic fungicidal. It exhibits in vitro and in vivo efficacy against a wide range of fungi including aspergillus and candida species. Caspofungin is only approved for invasive aspergillosis for patients who are refractory to or do not tolerate conventional antifungal agents.[21]

Possible histamine mediated symptoms have been reported in patients receiving caspofungin including rash, facial swelling, pruritus, sensation of warmth etc. Fever, phlebitis, nausea, vomiting and diarrhoea are other side effects. Raised alkaline phosphatase, reduction in hemoglobin and serum potassium are other adverse effects.[21]

The dosage of caspofungin is 70 mg on day one followed by 50 mg daily.[21]

Voriconazole

Voriconazole is well absorbed orally with a bioavailability of 96%, allowing patients to be switched between intravenous and oral administration.

The most common side effects are transient visual disturbances, fever, rash, vomiting, diarrhoea, headache, pain in abdomen, peripheral edema etc.

Antimicrobial agents in the pipeline

Several new agents are currently under development, the most notable being the glycopeptides dalbavancin, otritivancin and telavancin, the carbapenem doripenem, cephalosporins ceftobiprole and dihydrofolate reductase inhibitor iclaprim. Some of them may be available in the future for the use in clinical practice.

Conclusion

Nosocomial infections occur worldwide and affect both developed and resource – poor countries. Infections acquired in health care settings are among the major causes of death and increased morbidity among hospitalized patients. Important patient factors influencing acquisition of infection include age, immune status, underlying disease and diagnostic as well as therapeutic interventions. Overcrowded hospitals especially burn units, NICUs and PICUs facilitate development of nosocomial infections. Hospital acquired infections are usually caused by multidrug resistant organisms as they are exposed to several antimicrobial agents. Knowledge of surveillance data on a regular basis of predominant organisms in the hospital and intensive care units is very essential to choose the empiric therapy for nosocomial infections. Still failure of the drugs to treat the nosocomial infection is the common problem worldwide. New antimicrobial agents with unique mechanisms or improved antimicrobial activity compared with agents in the same class are needed to treat resistant pathogens as they become more prevalent among hospitalized patients. Several agents are currently under development and are likely to be available for clinical use in near future.

Points to Remember

- ***Nosocomial Infection is among the most difficult problems confronting clinicians who deal with severely ill children. NIs occur world wide and affect both, developed and developing countries.***
- ***Many factors are potential routes of infection and the transmission of drug resistant bacteria among crowded hospitals where poor infection control practices may facilitate transmission.***
- ***New antimicrobial agents with unique mechanisms or improved antimicrobial activity compared with agents in the same class are needed to treat resistant pathogens as they become more prevalent among hospitalized patients.***
- ***Linezolid, Quinupristin – Dalfopristin, Daptomycin, Tigecycline, Colistin, Casofungin, Voriconazole are recently launched molecules in the market and are available for use in the clinical practice. Their use in defined clinical situations is promising.***
- ***Several new agents are in the pipeline, the most notable being glycopeptides, dalbavancin, otritivancin and telvancin, the carbapenem doripenem, cephalosporins ceftobiprole and dihydrofolate reductase inhibitor iclaprim. Some of them may be available in the future for the use in clinical practice.***

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DRUG PROFILE

QUINOLONES IN PEDIATRICS

Jeeson C Unni

Abstract: *The antibacterial spectrum, pharmacodynamics and pharmacokinetics of the quinolones make them suitable agents for treatment of various pediatric infections. The fear of these agents inducing injury to developing joints in children have been allayed to a large extent due to lack of evidence. Hence there is no reason to avoid their use when specific indications exist. There are many conditions for which this group of antibiotics may be prescribed in children including shigellosis, pyelonephritis, typhoid fever and topically in ear and eye infections, to name a few. There are reports of increasing antimicrobial resistance to this group of antibiotics in the West. This, along with the persistent concern of adverse effects, which are still not being totally ruled out by experts, restrict the use of quinolones in pediatrics. These drugs are not considered as first line medication and its use is invariably prefixed with a caveat. Currently ciprofloxacin has the most evidence for safety and efficacy in children and therefore is listed in the IAP Drug Formulary along with nalidixic acid and ofloxacin. Use and safety of newer quinolones in children needs further evaluation and review.*

Key words: *Quinolones, Fluoroquinolone, Ciprofloxacin, Cfloxacin, Norfloxacin, Antibacterial spectrum, Safety, Indications, Dosage, Pharmacokinetics, Drug interactions, Adverse effects.*

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Though the IAP Drug Formulary states that quinolones should be used in children only for severe infections and for clear indications[1] as a second line drug in situations where the benefits outweigh the risk of arthropathy, pediatricians are increasingly using these antibiotics to manage pediatric infections. The indications for which a fluoroquinolone (ie, ciprofloxacin) is licensed by the US Food and Drug Administration for use in patients younger than 18 years are complicated urinary tract infections, pyelonephritis and postexposure treatment for inhalation anthrax. Nonetheless, approximately 520000 prescriptions for fluoroquinolones were written in the United States for patients younger than 18 years in 2002; 13 800 were written for infants and children 2 to 6 years of age, and 2750 were written for infants younger than 2 years.[2] As pressure to use quinolones for infections in pediatric patients increases, an attempt is made to review current data to assess options.

The first quinolone, nalidixic acid (1st generation), was introduced in 1962. Since then, structural modifications have resulted in second- (Class I - eg. norfloxacin and Class II eg. ciprofloxacin and ofloxacin), third- (eg. levofloxacin, gatifloxacin and moxifloxacin), and fourth- (eg. trovafloxacin) generation quinolones, which have improved coverage of gram-positive organisms. The 3rd and 4th generation quinolones have not been adequately studied in children.

Mechanism of action

Quinolones are bactericidal. The mode of action of quinolones involves interactions with

both DNA gyrase, the originally recognised drug target, and topoisomerase IV, a related type II topoisomerase.[3] In a given bacterium these 2 enzymes often differ in their relative sensitivities to many quinolones, and commonly DNA gyrase is more sensitive in gram-negative bacteria and topoisomerase IV more sensitive in gram-positive bacteria. The DNA gyrase is responsible for counteracting the excessive supercoiling of DNA during replication or transcription. This supercoiled state is essential to the well-being of bacteria as it enables them to accommodate their chromosome (1300 mu long) within the confines of their cell envelope (2 mu X 1 mu). However, the bactericidal action of nalidixic acid and most other quinolones can be abolished if protein synthesis is inhibited by chloramphenicol or RNA synthesis is inhibited by rifampicin. With ofloxacin and ciprofloxacin the situation is more complicated because protein or RNA synthesis inhibition does not completely abolish their bactericidal effects. The newer quinolones thus exhibit a qualitative difference from most other quinolone antibacterial agents in that they possess an additional mechanism of killing bacteria that is not possessed by the older, lesser active drugs.[4] Although human cells do not contain DNA gyrase, they do contain a topoisomerase enzyme that functions in a similar manner. This mammalian enzyme is not affected by bactericidal concentrations of quinolones and therefore these drugs kill bacteria without harming human cells. It is unclear how inhibition of DNA gyrase leads to bacterial cell death. Both rapid and slow growing organisms are inhibited by quinolones.

Anti bacterial spectrum

Quinolones have a very good spectrum of activity.[5, 6] They are active against several clinically important aerobic Gram negative bacilli like those belonging to enterobacteriaceae (eg. E coli) and Pseudomonas aeruginosa. Ciprofloxacin is twice as active against P aeruginosa as trovafloxacin and levofloxacin and 4 times as active as ofloxacin.[7] The quinolones are also active against Gram positive cocci like S pneumoniae, S aureus and beta haemolytic streptococci. Although they are more active against staphylococci than streptococci, resistance is known to readily develop while on therapy. H influenzae, Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumoniae are also susceptible. Anaerobic cover is limited.

Moxifloxacin is one of the first of a new generation quinolones with enhanced activity against gram positive bacteria. It is not yet licensed for use in children but has potential to be an important agent in treatment of bacterial infections of the respiratory tract, resistant to other oral agents.

Pharmacokinetics

Quinolones are well absorbed following oral administration, with moderate to excellent bioavailability.[8,9] Serum drug levels achieved after oral administration are comparable to those with intravenous dosing, which allows an early transition from intravenous to oral therapy and a potential reduction of treatment costs.

Food does not impair the absorption of most quinolones. However, quinolones chelate with cations such as aluminum, magnesium, calcium, iron, and zinc. This interaction significantly reduces absorption and bioavailability, resulting in lower serum drug concentrations and less target-tissue penetration.

Elimination half-lives for the quinolones vary from 1.5 to 16 hours. Therefore, most of these drugs are administered every 12 to 24 hours. The quinolones are eliminated by renal and nonrenal routes. To avoid toxicity, dosages often need to be adjusted in patients with renal or

hepatic impairment. The majority of quinolones are excreted through the kidney; however, sparfloxacin, moxifloxacin, and trovafloxacin are excreted via the liver. Quinolones are widely distributed throughout the body. Tissue penetration is higher than the concentration achieved in plasma, stool, bile, prostatic tissue and lung tissue.

The quinolones exhibit concentration dependent pharmacodynamics with the greatest bacteriocidal effect occurring when maximum peak concentrations are obtained.[8,9] Additonally, they exhibit a prolonged post-antibiotic effect of 1-2 hrs.[9] Therefore, organisms may not resume growth for 2-6 hours after exposure to ciprofloxacin, despite undetectable drug levels. Most quinolones, like ciprofloxacin and ofloxacin (norfloxacin is an exception) are concentrated within human neutrophils, which may explain its effectiveness in treating mycobacterial infections. Quinolones also penetrate well in urine and kidneys when renal clearance is the route of drug elimination. Penetration into prostatic fluid, saliva, bone, and cerebrospinal fluid does not exceed serum drug levels. Because CSF levels of quinolones are predictably poor, these agents are inadequate for treatment of meningitis. Differences in pharmacokinetic properties are emerging as important determinants in distinguishing among clinical uses of individual new quinolone antimicrobial agents.[10]

When administered along with other classes of antibiotics, such as beta-lactams and aminoglycosides, the quinolones are not predictably synergistic.[9] Although the effects of most combinations are indifferent or additive, ciprofloxacin and rifampin appear to be antagonistic against Staphylococcus aureus.[11]

Issues of safety for use in children

The class label warnings against quinolone use in children stem from drug studies in juvenile animals in which there was documented reversible joint toxicity, especially to the cartilage of growth plates.[12,13] This led to labeling precautions against their use in children, except on a compassionate basis.

Studies on nalidixic acid in children provided the first insight into the adverse-event profile and particularly the effects of this quinolone on pediatric joints. These initial clinical data suggested that there might be significant interspecies differences regarding the incidence and severity of toxicity associated with the use of quinolones. In 1989 the FDA gave permission to study the use of ciprofloxacin in 2 subpopulations – children with cystic fibrosis and those with neutropenia following anti-cancer chemotherapy. European trials also provided data on safety and efficacy of quinolones in children.

Study of children on ciprofloxacin showed that the mild to moderate arthralgia, that may develop in a very small number of patients, resolves spontaneously[12,14] and the review of data on children given ciprofloxacin, ofloxacin or nalidixic acid concluded that concern regarding chondrotoxicity is not justified.[13] Most reported musculoskeletal events associated with quinolone use have been of moderate intensity and were transient.[15-17] Further, there was no demonstrable difference in musculoskeletal toxicity between patients receiving ciprofloxacin or ofloxacin and azithromycin.[18]

Clinical uses

Although the association between quinolones and pediatric arthropathy is weak, it is prudent to use these antibiotics only when safer alternatives are not available.[19] The quinolones should preferably not be used as first line drug in pediatrics and the present day indications for quinolones in pediatrics would include:

1. Serious Gram negative infections resistant to other agents.[2,20]

2. Multi-drug resistant typhoid fever - however, the evidence is not overwhelming.[21] A Cochrane review identified 33 trials of which 3 were exclusively in children and reported that data of its use in pediatrics was limited.[22] Quinolones-resistant S paratyphi and S typhi are being reported from India of late.[23]

3. Chronic suppurative otitis media[6] or malignant otitis externa[20], especially that caused by P aeruginosa. Oral and/or topical applications may be used though topical preparations are preferred in these conditions.[24]

4. UTI when conventional agents have failed or are less desirable (eg. toxicity/ hypersensitivity concerns), or when resistance is high – especially infection caused by P aeruginosa or other multidrug-resistant, Gram-negative bacteria[2] Though resistance rates of uropathogens to quinolones are low, they are emerging as shown in various studies from around the world.[25,26]

5. Alternative therapy for multi-drug resistant invasive shigellosis, salmonellosis and campylobacter.[2] However, recent recommendations of the IAP-UNICEF Program on Evidence-based Management of Diarrhea emphasise the need to restrict use of antimicrobials to children with gross blood in stools or Shigella positive culture, cholera, associated systemic infection, or severe malnutrition.[27] Ciprofloxacin is safe and effective in treating GI infections[6] and may be considered for empirical therapy in outbreaks of multi-drug resistant shigella dysentery, even in resource poor settings.[28] High resistance to cotrimoxazole and nalidixic acid and decreasing susceptibility to ciprofloxacin is being reported in the sub continent.[29]

6. Alternative to rifampicin for nasopharyngeal eradication of N meningitidis.[30]

7. Children with cystic fibrosis who are prone to respiratory infections caused by P aeruginosa. Oral ciprofloxacin is shown to be as efficacious as betalactam and aminoglycoside combination for this indication.[5] Oral therapy allows domiciliary treatment and reduces cost and is found to be well tolerated by these children for long term use.[6]

8. Anthrax, plague, tularemia and Q fever. However, doxycycline is superior to quinolones in treating all these conditions.[1]

Therefore, it need not be re-emphasised that ciprofloxacin, norfloxacin, ofloxacin and other quinolones should only be used for serious infections and for clear indications. Because fluoroquinolones are so effective for the management of P aeruginosa infections, they have also been used on a compassionate basis even when these infections do not occur in a susceptible patient population.

Combination with other antibiotics

Combinations of quinolones with other antimicrobial agents have been extensively investigated.[31] Combining quinolones with rifampin, both given orally, for staphylococcal infections[31,32] reduces cost of treatment and hospital stay when compared with flucloxacillin or vancomycin therapy. Difficult to treat P aeroginosa infections may respond to combinations of antipseudomonas penicillins or meropenem with fluoroquinolones[31] and those involving infected orthopedic prosthesis are amenable to treatment with a combination of ceftazidime with ciprofloxacin[33] Quinolones in combination with parenteral third generation cephalosporins may have a synergistic effect against Escherichia coli, salmonella and other gram negatives.

Resistance to quinolones

Quinolone resistance has multiple mechanisms and could have significant clinical

impact. Mutations may occur rapidly during quinolone therapy and may be the most significant factor limiting the use of these antimicrobials. Although the newer quinolones, based on MIC data, show activity against gram-positive bacteria in vitro, pediatricians need to be cautious when treating life-threatening gram-positive infections with these drugs. Continued overuse of these antimicrobials in clinical medicine could promote gram-positive and gram-negative resistance and is likely to limit the effectiveness of the quinolones.[2,34] Overuse of a single agent will ultimately result in resistance to the entire class. The issue of rapid emergence of resistance to quinolones is of greater concern than its adverse effects.

Drug interactions[35]

Decreased absorption of quinolones is reported if didanosine or multivalent cations are administered concomitantly or less than 4 hours before or after a quinolone. Products that contain multivalent cations (calcium, aluminum, magnesium, iron, and zinc) include antacids, nutritional supplements, multivitamin and mineral supplements. Avoid concomitant use of quinolones and sucralfate. Quinolones may increase anticoagulant effects of warfarin. Therefore, prothrombin time should be monitored if warfarin or a warfarin derivative is used concomitantly with any quinolone. They may increase serum levels of theophylline and cyclosporine and prolong QTc if used with antiarrhythmics and cisapride.

Adverse effects[20,35,36]

The concerns regarding musculo-skeletal side effects have been discussed earlier. Most frequent adverse events are GI related and include diarrhoea, vomiting and abdominal pain. Headache, dizziness, numbness, restlessness, difficulty falling asleep or staying asleep, skin rash, itching, difficulty breathing or swallowing, swelling of the face or throat, yellowing of the skin or eyes, dark urine, pale or dark stools, blood in urine, unusual tiredness, sunburn, seizures, vaginal infection and vision changes have been reported. Eye drops may cause transient ocular irritation, including photophobia and burning. Otic use may be associated with pruritis, local irritation, burning, taste perversion, dizziness and earache.

Dosage

Nalidixic acid

Urinary tract infection (UTI) due to susceptible organisms: Oral: Adolescents: 1 gram suspension or tablet PO every 6 hours for 1 to 2 weeks. Maintenance dose of 500 mg PO every 6 hours. Children and infants >= 3 months: The recommended total daily dosage for initial therapy is 55 mg/kg/day PO, administered in four equally divided doses. For prolonged therapy, the total daily dose may be reduced to 33 mg/kg/day PO.

Urinary tract infection (UTI) prophylaxis in children: Oral: Children and infants >= 2 months to 2 years: A dose of 30 mg/kg/day PO in two divided doses has been recommended.

Maximum Dosage Limits: Adolescents: 4 g/day PO. Children and infants >= 3 months: 55 mg/kg/day PO. Infants < 3 months: Safe and effective use has not been established.

Patients with hepatic impairment: Exercise caution when using nalidixic acid in patients with liver disease, however, no specific dosage adjustments are indicated. Patients with renal impairment: Decrease the dose by half in patients with a CrCl less than or equal to 20 ml/min.

Ciprofloxacin

Dosage: Neonates 10mg/kg 12 hrly orally or IV; children 15-30 mg/kg/24hr in 2 divided

doses oral or IV (Maximum single dose IV 400mg and oral 750mg)

Dose adjustment in renal or liver failure: In severe impairment (creatinine clearance <20ml/ minute/1.73sqm) total daily dosage may be reduced by half, although monitoring serum levels provides the most reliable basis for dose adjustment. No adjustment in impaired hepatic function.

Corneal ulcers - apply throughout the day and night. First day -2 drops every 15min for 6hr followed by 2 drops every 30min for the rest of the day. 2nd day - 2 drops every hour and from 3rd to 14th day - 2 drops 4th hrly.

Superficial infections of eye - 1-2 drops 4 times daily till 48 hrs after the eye is clinically normal (use for max. of 21 days)

Ofloxacin

Dosage: Eye drops - >1yr 1 drop 2-4hrly for 1st 48hrs and then 4 times daily till 2 days after healing is achieved (max 10 days).

Ear drops - Otitis externa - 1-12yr 5 drops and 12-18yr 10 drops to affected ear(s) 2 times daily for 10 days. CSOM - >12yr 10 drops to affected ear(s) 2 times daily for 14 days. AOM with perforation or with tympanostomy tubes 1-12yr - 5 drops to affected ear(s) 2 times daily for 10 days.

IV and oral - 10-15mg/kg/day in a single dose or divided twice daily.

Conclusions

There have been many unresolved issues regarding use of quinolones in pediatric practice and some doubts still remain. Well-defined studies need to be done to define optimal treatment schedules for various infactions. So much so that, even today, it is advisable to think twice before initiating treatment with quinolones as some of the side effects in children, such as nephrotoxicity[37], not described until recently, may only be seen with wider use of these antibiotics in the pediatric population.[38] Parents of children who are receiving quinolones should be made aware of the possible development of arthralgias, so that evaluation of the children can be carried out immediately.

If used judiciously, the new quinolones, because of their antibacterial spectrum and pharmacokinetic properties, may be considered not only for compassionate use but also for potential administration in children for the specified indications. Their use as alternative therapy may help prevent the development of bacterial resistance to standard antimicrobial therapy.

Points to Remember

- ***Fears of quinolones inducing sustained injury to developing joints in children have been allayed to a large extent due to lack of evidence.***
- ***But since concern of adverse effects have still not been totally ruled out by experts and there being increasing reports of rapid development of resistance to this group of drugs in the West, quinolones are not considered as first line medication for any pediatric illness and its use is invariably prefixed with a caveat.***
- ***Use of quinolones in pediatrics may continue to be restricted, till all issues are resolved, to the following indications -***
  - ***a) Serious Gram negative infections resistant to other agents***
  - ***b) Multi-drug resistant typhoid fever***
  - ***c) Chronic suppurative otitis media or malignant otitis externa***

d) UTI when conventional agents have failed or are less desirable, or when resistance is high – especially infection caused by P aeruginosa or other multidrug-resistant, Gram-negative bacteria

e) Alternative therapy for multi-drug resistant invasive shigellosis and salmonellosis

f) Alternative to rifampicin for nasopharyngeal eradication of N meningitidis

g) Children with cystic fibrosis who are prone to respiratory infections caused by P aeruginosa

h) Anthrax, plague, tularemia and Q fever. However, doxycycline is superior to quinolones in treating all these conditions

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DERMATOLOGY

PAPULAR URTICARIA

* ***Madhu R***

Abstract: *Papular urticaria is a common dermatological condition of childhood characterized by a chronic or recurrent itchy papular eruption caused by hypersensitivity reaction to the bites of various arthropods including mosquitoes, fleas and bedbugs, which happen to be the important causative agents throughout the world. It occurs due to the acquired sensitivity to the insect proteinaceous allergens. Type I and type IV hypersensitivity play a role. Most common in children 2 – 10 years of age, after which hyposensitisation occurs. Prevention of exposure to insect bites plays an important role in the managemaent of papular urticaria, which includes topical corticosteroids, antihistamines and systemic antibiotics when required.*

Keywords: *Arthropods, Bites, Hypersensitivity.*

Synonyms : Prurigo simplex acuta infantum, Lichen urticatus, Acute prurigo, Strophilus infantum, Urticaria papulosa infantum, Lichen simplex acutus.[1] Commonly referred to as mosquito bite allergy or insect bite allergy (IBA).

Papular urticaria is a common dermatological condition of childhood characterized by a chronic or recurrent itchy papular eruption caused by hypersensitivity reaction to the bites of various arthropods including mosquitoes, fleas and bedbugs, which happen to be the important causative agents throughout the World.[2] It is most commonly seen in children between 2 to 10 years of age.[3] Immediate reactions are due to histamine, serotonin, formic acid or kinins. Delayed reactions are manifestations of the host's immune response to the injected arthropod salivary protein allergen.[4] The most difficult task in the diagnosis of papular urticaria is in convincing the parents that the lesions are related to a bite reaction, because they most often deny the presence of any arthropod or question why only the child should be affected and not the other family members.

Etiopathogenesis

Papular urticaria was found to be associated with insect bites as early as 1813 and was later described by Brocq in 1894.[1] It is generally regarded to be the result of a hypersensitivity reaction to bites from insects, such as mosquitoes, gnats, fleas,mites, bedbugs,caterpillars and moths.[5] Mites or fleas from dogs or cats are common, but mites from birds, rats may also cause papular urticaria. Hence, a proper history regarding living conditions, contact with pet animals, birds and rhodents should be taken.[6] Mites that may be present in stored food products like flour, grains and dried food have also been implicated.[2] There is a seasonal incidence depending on the habits of the biting insect. Lichen urticatus presents throughout the year, but is more in summer and rainy season when insect population is more in localities where they remain undisturbed. Moreover rainy season is a favorable time for the breeding of insects.[7,8] In most groups of flies, it is only the female

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insects which bite, the reason being that the sucked blood acts as a good source of concentrated protein that enables them to bring their eggs to maturation rapidly.

Body heat, carbon dioxide in exhaled air (eg. ticks, fleas, bed bugs) and displacement of air or vibrations caused by the host (eg. fleas) are the various means by which arthropods are attracted to the host.[9] Mosquitoes are attracted to bright clothing, heat, humidity, human odours, particularly of young children. Carbon dioxide released mainly from the breath but also from the skin is a long range attractant for mosquitoes.[10] Estrogen and L – lactic acid in human sweat have been found to attract mosquitoes.[2] Anhidrotic subjects are unattractive to mosquitoes. Dilapidated housing provides an ideal habitat for bed bugs. Persons in contact with pet animals are prone for flea bites. Individuals moving into premises which were kept vacant, but previously occupied by pet dogs or cats may experience severe attacks by the fleas.

The hypersensitivity reaction to the antigens deposited during the insect bites in most individuals follows a familiar immunization sequence from that of no response in immunologically naïve individuals through delayed and immediate responses to immune tolerance.[3] These reactions usually follow the following pattern:

1. At initial stage, the individual is still immunologically naïve and shows no reaction to any bite experienced.
2. The typical bite reaction is a type IV delayed hypersensitivity reaction, usually seen as an itchy inflammed maculopapule that appears 8- 72 hrs after the bite and persists for several days. Once sensitized , the person may subsequently show anamnestic reactions to bites by the same species or related species of insect for the rest of life.
3. After repeated bites for a further period which may be months or years after the initial event, an immediate type I reaction (a small weal of about 3 -5 mm) appears about 20 minutes after the bite. A type IV delayed reaction occurs several hours after the bite, which persists for several days.
4. Only the immediate, type I, weal develops, but not the delayed response.
5. Eventually, tolerance is acquired and no reaction occurs.

Immunological basis of hyposensitisation is still not clear. Development of blocking antibodies and a reduction in the amount of specific antibody bound to tissue mast cells probably play a role. Suppressor T cells which act as negative regulators, inhibiting both cell mediated and humoral immune responses, also contribute to this immunomodulation.

Being an acquired specific sensitivity, papular urticaria is rare in infants. It is commonly seen in children between 2 and 10 years of age. However, older age groups may be affected too. People migrating to a new geographic area get exposed to the arthropods for the first time in later life, develop papular urticaria. This phenomenon is commonly observed in non resident Indians, when they come to India. Sensitivity may persist into adolescence or later life in atopic individuals. Exaggerated insect bite hypersensitivity occurs in HIV infected individuals and in cancer patients on chemotherapy or radiation.[2]

Clinical features

Lesions tend to have a characteristic distribution and configuration depending on the biting insect and the clothing habits of the host. Mosquitoes and biting flies usually attack the exposed areas of the body. Flea bites are often multiple and grouped together in a linear or

irregular clusters on the forearms, legs or on areas where clothing fits snugly (lower abdomen, waist, buttocks and thighs). The classic linear configuration of flea bites (the breakfast, lunch and dinner sign which is also present in bedbug bites) is caused by the tendency of fleas to jump and crawl rather than fly.[10] Bed bug bites are seen mainly on the buttocks, back and sides of the trunk, where the body comes in contact with the bed or chair. Eruptions are less often found on the face and neck. Axilary, genital and perianal areas are usually spared.[11]

Papular urticaria starts as an urticarial wheal at the site of bite to be succeeded by a firm pruritic papule that persists for several days. Papules may be surmounted by a thin vesicle. Often, there is a central hemorrhagic punctum. Papules, usually of 3-10 mm size are grouped into clusters and develop in crops at irregular intervals and as they are intensely pruritic, excoriation and crusting occurs. Apart from the direct insect bite, papules may also occur as a result of autosensitisation. Sometimes, bullae may present on the lower legs. Rubbing and scratching may induce eczematisation. Secondary infection is a common complication and may manifest as impetigo and cellulitis. If there is no secondary pyoderma, the lesions heal in about 1 to 2 weeks leaving residual hyperpigmentation or hypopigmentation surrounded by hyperpigmentation. Recurrent episodes are common in the presence of ongoing exposure to the offending insects. When a fresh crop of papules occurs, there is a reactivation of the old lesions.

Differential diagnosis

The differential diagnosis of papular urticaria includes scabies, papular acrodermatitis of childhood (PAC), dermatitis herpetiformis, milaria rubra, id reaction, urticaria and drug eruption. Characteristic distribution and family history would go in favour of scabies. Papular acrodermatitis of childhood (Gianotti – Crosti syndrome), PAC is a benign self – limited condition characterized by erythematous, monomorphous papules and papulovesicles distributed symmetrically over the face and extensor aspects of the extremities, usually sparing the trunk, which may be caused by Epstein Bar virus, Parvovirus B19, Rota virus, Cytomegalovirus, Coxsackie viruses, HHV6 and Hepatitis B virus. It occurs predominantly in children between the ages of 1 and 6 years. PAC is usually asymptomatic, although mild pruritus may be present at times. Prior to the onset of exanthem, there may be a prodrome of upper respiratory symptoms, fever and lymphadenopathy. Lesions resolve over a period of 8 - 12 weeks. Post inflammatory hypopigmentaion may be present for several months. Dermatitis herpetiformis may occur in children and is characterized by intensely pruritic grouped vesicles on an erythematous base. As the itching or burning sensation precedes the onset of new lesion by 8-12 hours, only excoriated papules and crusts may be seen.

Treatment

Prevention of further insect bites is the most important step in the management of papular urticaria. Child should be advised to wear protective clothing with long sleeves and long pants. Use of insect repellants and mosquito nets is advocated. In cases of suspected bedbugs or flea bites, fumigation of the home should be done. Clothes and bedding should be laundered before and after treatment and dried in good sunlight. Pet animals should be treated with insecticidal shampoos.

The goal of symptomatic treatment is to reduce and prevent inflammation. Topical corticosteroids – hydrocortisone or clobetasone may be used in young children, while fluticasone or mometasone cream or ointment may be used

in older children for a period of two weeks. If infected, a combination of fluticasone and mupirocin topically and appropriate systemic antibiotics should be given. When therapy with topical steroid is ineffective or if there is severe inflammation at the onset, a short course of oral prednisolone started in a dosage of 1mg/ kg and tapered over 10 days.[11] Pruritus is controlled by antihistamines such as cetrizine, loratidine or fexofenadine. In case of severe itching, sedative antihistamines such as diphenhydramine and hydroxycine are preferred. Use of prophylactic cetrizine benefits children with recurrent and exuberant bite reactions.[12] Topical application of calamine lotion could be soothing to the child.

Use of insect repellants

DEET (N,N – diethyl – 3-methy benzamide) is the most effective topical insect repellant available that has a broad spectrum action against mosquitoes, biting flies, chiggers, fleas and ticks. It is considered that products with <10% DEET are safe for children.[12]

Guidelines for the safe use of insect repellants in children [10, 13]

Do's

- Read and follow all package directions and precautions
- Use aerosols or pump sprays for skin and for treating clothing. These products provide even application.
- Use liquids, creams, lotions, or sticks to apply more precisely to exposed skin.
- Apply sparingly to the face, and avoid contact with the eyes and mouth.
- After outdoor activity, wash DEET-covered skin with soap and water.
- Always keep insect repellents out of the reach of small children.

Don't

- apply to eyes, lips, or mouth, or over cuts, wounds, or irritated skin.
- overapply or saturate skin or clothing.
- apply to skin under clothing.
- apply more often than directed on the product label.
- apply to infants under 2 months of age.
- apply to the hands of young children.

Dr. Anne-Marie Irani of Virginia Commonwealth University, during her talk on New Research in Asthma, Eczema, and Urticaria in AAP 2006 Annual meeting, suggested the pmnemonic "SCRATCH" for diagnosis and treatment of papular urticaria.[14]

S - Symmetrical eruptions

C - Crops or clusters of lesions

R - "Rover" (a pet), although having a pet — or not having a pet — does not necessarily mean that lesions will develop. (The fact that the eruptions can be delayed make it difficult to identify any single pet exposure.)

A - Age usually limited to 2-10 years old (It is rare for sensitization to occur before 2 years.)

T - Target lesions can be the predominant form and time is required for presentations and resolution

C - "Confused" parent - Not able to identify exposure

H - Household with single patient affected (This reiterates the fact that sensitization is required for such a reaction to occur - not all family members will react to the same exposure [bites]).

Points to Remember

- ***The main anchor of treatment of papular urticaria is in the prevention of insect bites.***

- ***It is most often a frustrating experience for the child, parents and for the physician, when it comes to convincing the disbelieving parents about the etiology.***
- ***Hence, it is imperative to counsel the child and the parents regarding the importance of prevention and protective measures against insect bites, apart from providing symptomatic treatment with topical corticosteroids and systemic antihistamines.***

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CLIPPINGS

Lisa Ross DeCamp, Julie S. Byerley, Nipa Doshi, Michael J. Steiner. Use of antiemetic agents in acute gastroenteritis - A Systematic Review and Meta-analysis. Arch Pediatr Adolesc Me. 2008;162(9):858-865.

Ondansetron therapy decreases the risk of persistent vomiting, the use of intravenous fluid, and hospital admissions in children with vomiting due to gastroenteritis. Future treatment guidelines should incorporate ondansetron therapy for select children with gastroenteritis.

RADIOLOGIST TALKS TO YOU

CEREBRAL INFARCTION

**** Vijayalakshmi G***
***** Elavarasu E***
****** Venkatesan MD***

Infarction of the brain is not common in children. The commonest etiology of atheroma in the adults does not pertain to children. One frequent cause in children is dehydration or shock and hypoperfusion of the brain. This is more likely to occur in children under two years of age. In children, ischemia should also prompt a search for other disorders like congenital and acquired heart disease or infections like tonsillitis, meningitis or malaria, that give rise to emboli. Other rare diseases to be considered are arteritis (Takayasu disease, Moya Moya, SLE and PAN) and hematological disorders like sickle cell disease, polycythemia and coagulopathy.

Cerebral infarction manifests as convulsions, paresis or stroke. But these clinical signs do not always mean infarction. Imaging with CT or MRI is therefore required to exclude other causes like masses and granulomas. Quite often there maybe no known cause for infarction.

Figs.1 to 3 are that of a 4 year old child with hemiplegia. There is a homogenous hypodensity in the temporal and parietal regions on the right. You can see that both white and grey matter are involved. There is no white and grey matter differentiation. There is no sulcal-gyral differentiation. The extent of this lesion defines the territory of the middle cerebral artery. Note that the anterior portion (Fig.1) near the midline, served by the anterior cerebral artery, is not involved. Similarly the posterior portion near the midline is spared as it is supplied by the posterior cerebral artery. Fig.3 is a more superior section that shows an uninvolved paramedian cerebral parenchyma that is supplied by the anterior cerebral artery. The distribution of the infarct will therefore point to the obstructed artery.

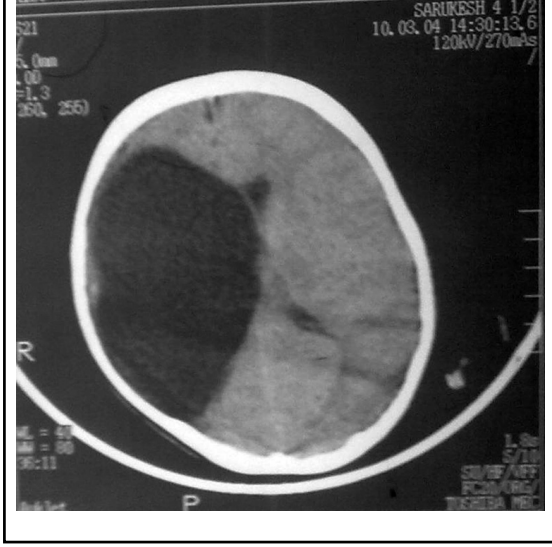

Fig.1. MCA territory infarction-Parietal lobe

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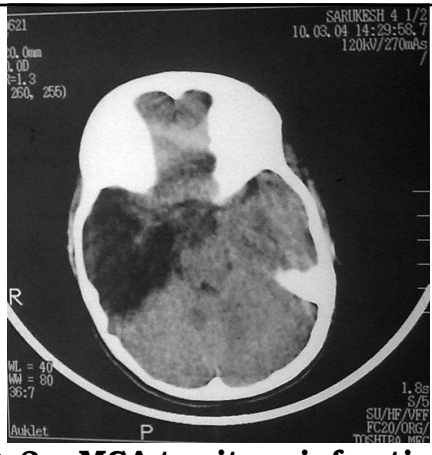

Fig. 2. MCA territory infarction - Temporal lobe

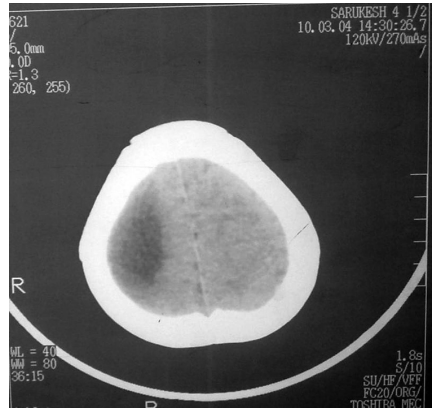

Fig. 3. MCA territory infarction – High parietal section

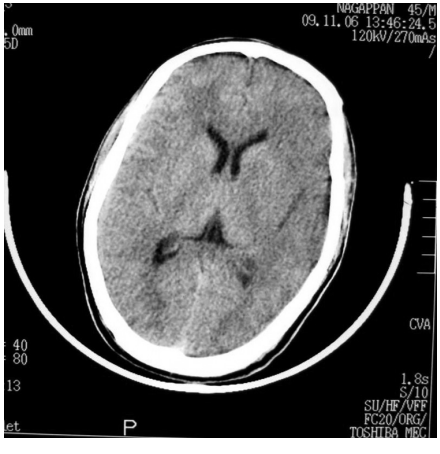

Fig. 4. Early infarction- Left MCA territory

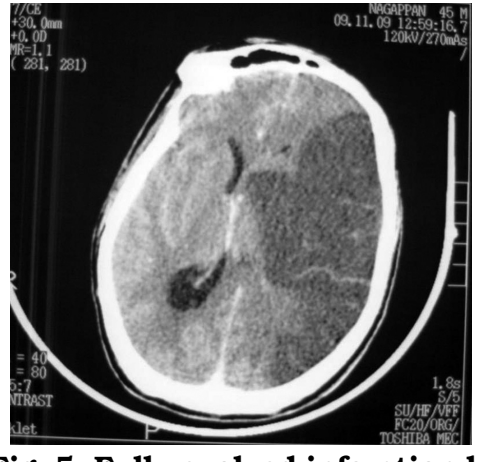

Fig. 5. Fully evolved infarction left MCA territory in the same patient

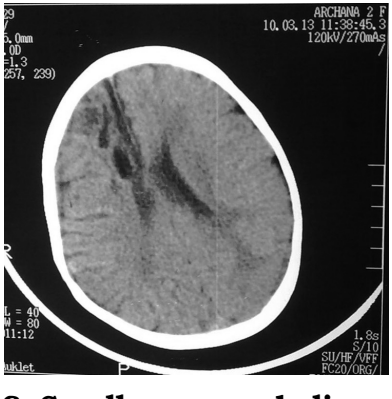

Fig. 6. Small porencephalic cysts in right frontal region

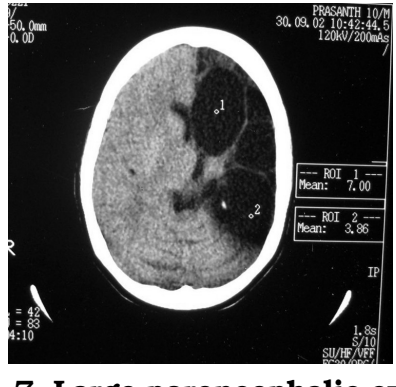

Fig. 7. Large porencephalic cysts in left ACA and MCA territories

Figs.1 to 3 are those of a fully established infarct. But when ischemia just begins to set in there are certain subtle CT findings that match the pathological events that ischemia initiates. Ischemia causes swelling of cells in both grey and white matter due to alteration in cell membrane permeability and accumulation of intracellular water. This is called cytotoxic edema. It leads to mild reduction in the density of grey matter which is responsible for certain subtle signs of early infarction that you should look for. If you see Fig. 4 carefully you will notice that there is an effacement of the sulcal gyral pattern on the left, though there is no clear cut hypodensity as in Fig.1. There is a shade of grey through out the middle cerebral artery territory, which washes out certain CT landmarks like the internal and external capsules. Therefore the basal ganglia and insular cortex are not made out separately. These are early ischemic changes that are likely to be missed. Now, look at the CT repeated (Fig.5) three days later. It shows a fully evolved infarct in the MCA territory. Now it is vasogenic edema due to leakage of fluid from damaged capillaries that is responsible for the further reduction in density of an infarct.

Physicians treating adults may not totally rely on radiological signs to start treatment for hemiplegia, as thrombosis or emboli are the common causes. In children, infarction is not only manifested as hemiplegia but also as convulsions. Therefore CT is essential to make a diagnosis of infarction. Further, thrombolytic treatment requires the absence of hemorrhage (seen as white areas) and imaging is absolutely essential for this in both adults and children.

Some of the ischemic tissue surrounding an infarct may recover while the totally infarcted area undergoes liquefaction and remains as porencephalic cysts. These cysts may be small as in the right frontal lobe in Fig.6, or large involving entire vascular territories as in Fig.7. Fig.7 is that of a ten year old child having large porencephalic cysts in both middle cerebral and anterior cerebral artery territories on the left.

We will see more about ischemia and infarction in the next issue.

CLIPPINGS

Ketogenic diet for treatment of epilepsy Alexander L. Rogovik, and Ran D. Goldman, Can Fam Physician

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The ketogenic diet (includes 80% fat, 15% protein, and 5% carbohydrate), initially described by Hugh Conklin, a Michigan pediatrician, is a high–fat, low–carbohydrate, and normal–protein diet that has been used for the treatment of medically refractory childhood epilepsy since the 1920s. The ketogenic diet can be considered as an option for children with intractable epilepsy who use multiple antiepileptic drugs, and is a treatment of choice for seizures associated with glucose transporter protein deficiency and pyruvate dehydrogenase complex deficiency. However the diet's strictness, unpalatability, and side effects limit its use and adversely affect both patients' compliance and clinical efficacy.

CASE STUDY

NEONATAL PARAESOPHAGEAL HERNIA

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**Regunandan SR
***Venkatasaravanan S

Abstract: *Two cases of neonatal hiatus hernia with varied modes of presentation are discussed. The management of this rare condition is highlighted with a review of literature.*

Keywords: *Neonatal paraesophageal hernia, Gastric volvulus, Gastropexy.*

Paraesophageal hiatus hernia(PEH) is very rare in new born. It is found in 0.8% to 2.9% of patients undergoing upper gastrointestinal contrast studies.[1] Neonates present with vomiting, aspiration and dyspnea. In the newborn it can mimic esophageal atresia.[2] The upper gastrointestinal contrast study is diagnostic. Neonatal PEH is a surgical emergency because of the potential danger of gastric volvulus. We are reporting our experience on two cases of neonatal PEH.

Case Report 1

Twenty five days old male neonate with respiratory distress was referred as unresolving bronchopneumonia (Fig.1). A differential diagnosis of Morgagni's hernia and hiatus hernia was thought of. A lateral view of chest X-ray showed air fluid level in posterior mediastinum suggestive of hiatus hernia and was confirmed by barium study (Fig.2), which showed the herniation of oesophago- gastric junction, whole of stomach and part of duodenum into the thorax. Peroperatively the entire stomach was herniating

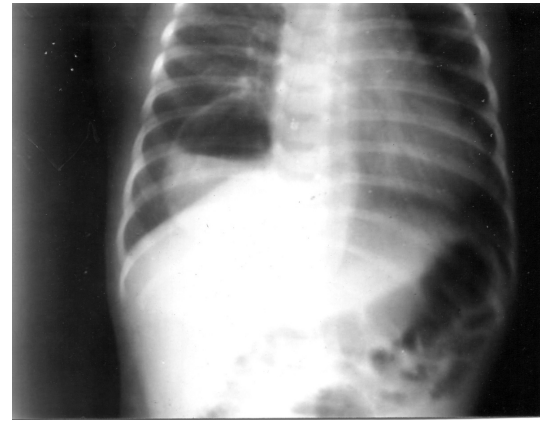

Fig.1. X-ray Chest: Features suggestive of consolidation right lower lobe

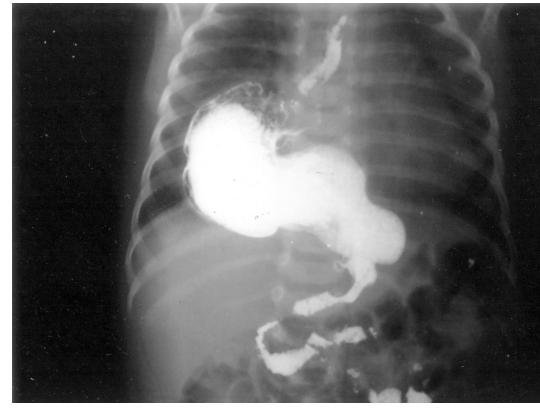

Fig.2. Barium Study: Hiatus hernia

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into the thorax. The stomach was reduced into the abdominal cavity. The oesophago- gastric junction was restored below the diaphragm and the patulous oesophageal hiatus was narrowed by approximating the two limbs of right crus of diaphragm. The stomach was fixed to the abdominal wall (gastropexy) to prevent volvulus of stomach which is imminent in a mobile organ. The baby was discharged with no postoperative problem.

Case Report 2

Twenty days old female neonate was brought with complaints of respiratory distress since birth. The baby was referred for surgical opinion with the diagnosis of space occupying lesion in the right lung with a chest X-ray (Fig.3). Diagnosis of hiatus hernia was suspected and confirmed by barium study . Peroperatively herniation of stomach, spleen and transverse colon were noted. The contents were reduced, the lax esophageal hiatus was narrowed and gastropexy was done (Fig.4). The neonate made an uneventful recovery and is on regular follow up.

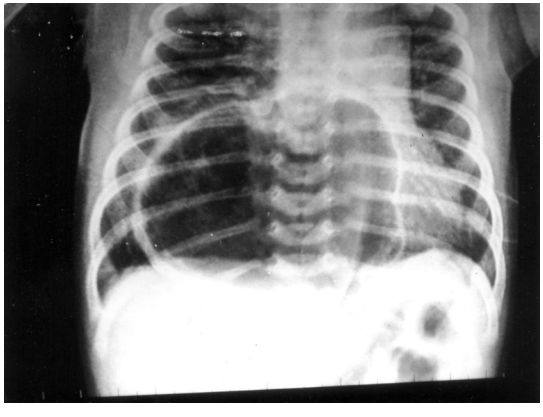

Fig.3. X-ray Chest: Hiatus hernia

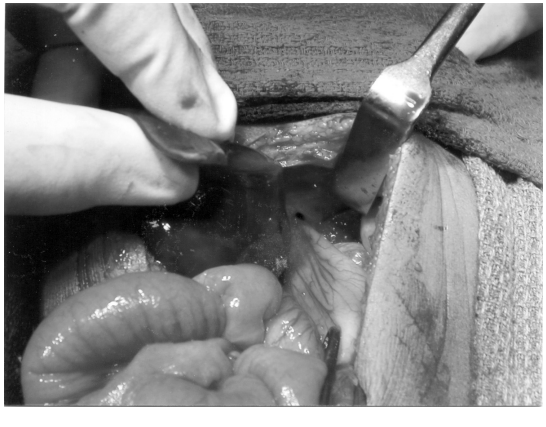

Fig.4. Per operative picture showing herniation of stomach, spleen.

Both infants were followed up for 10 months and are thriving well.

Discussion

Hiatus hernia is defined as herniation of abdominal contents into the thorax through the esophageal hiatus. Etiology is unknown.

There are 4 types of hiatus hernia. 1. Sliding hernia, 2. PEH, 3. Mixed and 4. PEH with other abdominal contents.Some cases with short esophagus may have autosomal dominant mode of inheritance[1]. PEH is also reported in siblings.[3] Hiatus hernia occurs due to lax esophageal hiatus aided by negative intrathoracic pressure and positive intra abdominal pressure. Associated anomalies are malrotation and cardiac defects.

Differential diagnosis includes congenital diaphragmatic hernia, congenital cystic adenomatoid malformation, bronchogenic cyst, neurenteric cyst, pericardial cyst, pulmonary sequestration and cystic teratoma.[1]. Investigation of choice is upper gastrointestinal contrast study. Clinical features include dyspnoea, vomiting and aspiration pneumonitis. The clinical features are mainly dependent upon the associated intrathoracic stomach and its degree of volvlus.[4] It can be associated with Marfan syndrome. Marfan syndrome should be considered in any infant with hiatus hernia with or without gastroesophageal reflux.[5] PEH can also present as hematemesis.[6]

Conclusion

Neonatal hiatus hernia is a rare disease. In the newborn period it can mimic esophageal atresia. Investigation of choice is barium meal study. Early surgical intervention is needed as there is a high risk of gastric volvulus.

Acknowledgement

We are thankful to Dr. Prabhakaran and Dr. Natarajan, Department of Pediatric radiology, ICH & HC, Chennai for their guidance and help in diagnosing the condition.

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CLIPPINGS

Shigemi Yoshihara. Early intervention for infantile and childhood asthma. Expert Review of Clinical Immunology March, 2010.

Asthma is a chronic airway inflammatory disease and it is accepted that early initiation of anti-inflammatory medication is beneficial for adult asthma. Pathological and epidemiological studies suggested that early intervention with anti-inflammatory drugs such as inhaled corticosteroids (ICS) should take place before preschool age, possibly between 1 and 3 years of age. However, the effect of early intervention using ICS in young children is considered controversial as several clinical studies have suggested that ICS does not alter the natural history of asthma in young children. Although there is limited and some negative evidence for the effect of ICS in young children, ICS remains the most effective medication for controlling asthma of the currently available drugs for all ages. Therefore, pediatricians should prescribe ICS to control the active symptoms of asthma, owing to the well-known, beneficial effects of ICS on decreasing the symptom burden of young children with asthma.

CASE STUDY

RESISTANT HYPERTENSION IN ACUTE POST INFECTIOUS GLOMERULONEPHRITIS

*** Suchetha Rao A**
**** Rathika Shenoy**
**** Kamalakshi Bhat**
***** Nutan Kamath**

Abstract: *In clinical practice hypertension in acute post infectious glomerulonephritis is responsive to standard therapy. We report resistant hypertension in a child requiring nine antihypertensive drugs including intravenous therapy and diuretics. The course was complicated by recurrent occipital headache, transient visual loss and encephalopathy.*

Keywords: *Resistant hypertension, Acute glomerulonephritis, Encephalopathy, Anti hypertensive therapy.*

Resistant hypertension defined as persistence of blood pressure (BP) above set goal even with concurrent use of optimal doses of three antihypertensive agents of different classes including a diuretic is reported mainly in elderly and obese.[1] Reports in pediatric population are limited to studies on children with chronic kidney disease (CKD) and isolated case reports.[2,3] We report resistant hypertension in a child following acute post infectious glomerulonephritis (PIGN) for its rarity. The course was complicated by recurrent episodes of transisent visual loss and encephalopathy.

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Case Report

A 12 year old, previously healthy boy was brought to the emergency department with generalized edema and reduced urine output of two days duration. There was no history of fever, hematuria, headache, blurring of vision and convulsions. No medical attention was sought for a sore throat he had two weeks ago. There was no family history of renal disease or hypertension. On examination, he was irritable with pulse 90/min, BP 140/102 mmHg and respiratory rate 28/min. His weight and height of 37 kg and 148 cm were between 25th and 50th percentiles in CDC2000 growth chart. The 95th and 99th percentiles of BP for his age and height were 123/81 and 131/89 mmHg respectively. There was anasarca including ascites. No flank masses or renal bruit were present. There was no cardiomegaly, murmurs or ejection click. Central nervous system and fundus examination were normal. There were no basal crackles. Child received sublingual nifedepine at admission. Investigations showed severe renal impairment with blood urea nitrogen (BUN) 167 mg/dL [27.83 μmol/L], serum creatinine 5.3 mg/dL [468.52 μmol/L] and estimated glomerular filtration rate (GFR) 13 ml/m^2/min. There was no hyperkalemia or acidosis. Urine analysis showed proteinuria, hematuria. Bilateral increased parenchymal echotexture with partial loss of corticomedullary differentiation was seen on renal ultrasonogram. Serum complement (C3)

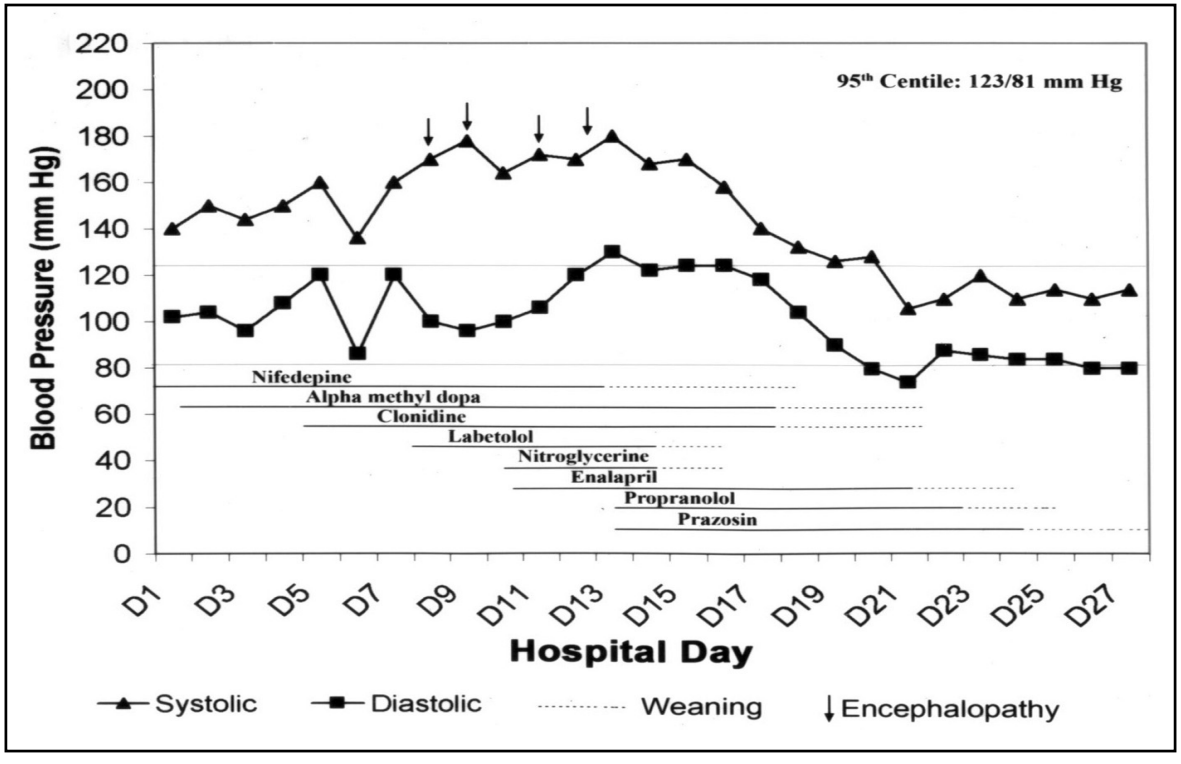

Fig.1. Average blood pressure and anti hypertensive therapy during hospital stay

was low (59 mg/dL) and anti streptolysin O titre negative.

A provisional diagnosis of acute nephritic syndrome in renal failure was made at admission with PIGN as etiology and rapidly progressive glomerulonephritis as a possibility in view of the severity of presentation. Peritoneal dialysis was initiated and his clinical and biochemical parameters were monitored. By 72 hours his urine output improved to 1.8 ml/kg/hr, BUN to 100 mg/dL [16.6 μmol/L], serum creatinine to 1.4 mg/dL [123.76 μmol/L], GFR to 48 ml/m^2/min and dialysis was stopped. However his hypertension was persistent was persistent and intravenous furosemide was added with modifications in antihypertensive therapy. His average BP recordings during the hospital stay and therapy are shown in Fig.1. Each drug was increased to the optimal recommended dose before another was added. The complications that occurred during the clinical course included encephalopathy in the second and symptomatic hypokalemia in the third week of illness. The encephalopathy was characterised by sudden occipital headache, loss of vision, generalized tonic clonic seizures and deterioration in sensorium. These episodes were recurrent and transient lasting about 30 minutes with normal vision and sensorium in between. Fundus examination did not show hemorrhages or exudate. Seizures were initially controlled with intravenous midazolam but subsequently required loading with phenytoin as the convulsions became frequent as hypertension was persistent. Computed tomography of head

showed effacement of cortical sulei and attenuation of white matter suggestive of cerebral oedema.

Given the significant difficulty in BP control despite clinical and biochemical improvement, he was evaluated further. Renal biopsy showed diffuse endocapillary proliferative glomerulonephritis with no tubulointerstitial changes, consistent with acute PIGN. Immunoflourescence revealed significant peripheral and mesangial granular deposits of IgG and C3. Echocardiogram and renal artery doppler studies were normal. Plasma renin activity and 24 hour urine catecholamines were normal. Antinuclear antibody was negative. In the third week of illness BP control was achieved with cessation of several drugs and child was discharged on prazosin. At third month follow-up serum C3 was normal and prazosin was stopped. His BP, cardiac, neurologic examinations and urine analysis continue to be normal in the one year follow-up.

Discussion

Acute PIGN is the commonest cause of diffuse proliferative glomerulonephritis the prototype being post streptococcal infection. In about 25-33% of post streptococcal glomerulonephritis hypertension is seen.[4] In clinical practice hypertension in acute PIGN is responsive to diuretics an standard antihypertensive therapy. In our case we started with oral nifedepine followed by alpha methyl dopa and both drugs were titrated upwards along with intravenous furosemide added on the third day of admission. As his estimated GFR suggested severe renal function impairment intravenous furosemide and angiotensin-converting enzyme inhibitor were deferred at admission. An intravenous anti hypertensive therapy was not considered in the absence of hypertensive emergency at admission especially as his renal functions were improving. Intravenous labetolol and subsequently nitroglycerine in preference over sodium nitroprusside and oral clonidine were added in the second week when the child developed encephalopathy. Encephalopathy occurring late in the course of illness was another unusual feature in this child. The neurologic manifestations clinically resembled posterior reversible encephalopathy syndrome but was not substantiated tomography.[5] By the end of second week of admission child was on nine antihypertensive drugs including intravenous therapy. The main adverse event noted in this child with multiple thrapy was symptomatic hypolalemia probably due to intravenous furosemide. The third week of illness saw rapid recovery with removal of several drugs and this as well as the treatment resistance seen in the second week remains unexplained.

Aggressive pharmacologic approach to hypertension is required to prevent progression in to renal disorders and for better long term cardiovascular outcomes. Availability of several classes of effective anti hypertensive drugs offer greater choices in therapy. However therapeutic approach remains empiric and the choice largely rests on the treating physician.[6] With the exception of hypertensive emergencies like encephalopathy it is preferred to start with a single drug, titrate it upwards before multiple drug therapy is initiated. There is lack of systematic assessment of multi drug combination even in adults.[1] Several mechanisms have been proposed for resistant hypertension in CKD which include activation of renin angiotensin system, refractory volume expansion, sympathetic activation, endothelial dysfunction and reduced renalase.[1,6,7] These may also be relevant in acute medical renal disorders with resistant hypertension. The management when multiple drugs are involved can be challenging to the clinician as the drugs differ in their

mechanisms of action and adverse reactions with potential additive and opposing effects.

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CLIPPINGS

Abdullah A. Yousef Adam Jaffe. The Role of Azithromycin in Patients with Cystic Fibrosis Paediatric Respiratory Reviews April, 2010.

Interest in azithromycin in the management of patients with cystic fibrosis has grown over the last decade. Uniquely this drug has both antibacterial and immune modulating effects which appear to be the reason for its clinical benefit as proven in several well designed clinical studies. In this review we discuss the proposed mechanisms of action of azithromycin and review the evidence for its clinical effectiveness and safety in cystic fibrosis.

NEWS AND NOTES

NEOCON- 2010

Annual Scientific Convention of National Neonatology Forum, Gujarat State.

Date: 18th & 19th September, 2010.

Contact

Dr. Maulik Shah, Associate Professor of Pediatrics,
Department of Pediatrics, Shri M.P.Shah Medical College,
JAMNAGAR (Gujarat-INDIA).

Mobile: 91-9428400389 Email: neocon2010@gmail.com

TRYPEDICON 2010

35th ANNUAL STATE CONFERENCE OF IAP-TNSC

Host : I.A.P. Trichy Chapter - TamilNadu State

Venue : Hotel Sangam, Trichy. Date : August 13th to 15th 2010

Dr. Sunil Srinivasan	Dr. Pannerselvam	Dr. Suresh Chelliah
Organising Chairman	Organising Secretary	Treasurer

Registration Fees

Dates	I.A.P (Rs.)	NON I.A.P (Rs.)	P.G. (Rs.)	Accompanying Person (Rs.)
16.05.10 - 31.07.10	3500	4000	3000	3250
01.08.10 - 15.08.10	4500	5000	4000	4250

1. Mode of Payment : Cash in Person / Cheque / D.D. 2. Senior citizens above 70yrs (as on 15.08.2010) Free (Age proof required) 3. Children below 5yrs (as on 15.08.2010) Free 4. Letter from H.O.D for P.G'S required. 5. Delegate Kit cannot be guaranteed for those registering after 01.08.2010 6. Add Rs 50/- extra for outstation cheques. 7. Accomodation and travel details are available in conference website.

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HOTEL SANGAM, TRICHY. Date : 12.08.10 Time : 9.00a.m. to 5.00p.m Lunch : 1.00p.m. to 2.00p.m.

Registrations for Trypedicon 2010 is a must for attending pre conference workshop.
Those who had already registered for the conference, Kindly register for Pre Conference workshop.

1. Neonatal Resuscitation Programme convenor Dr. Tiroumourougane Serane, Pondy
2. Sublingual Immunotherapy convenor Dr. Nagaraju, Chennai
3. Emerging infectious Diseases convenor Dr. Thangavelu, Chennai
4. Parenting for pediatricians convenor Dr. Yamuna, Chennai

You can Download the Registration Form for Conference and Pre Conference workshop from the Website
Other Details see www.trypedicon2010.com

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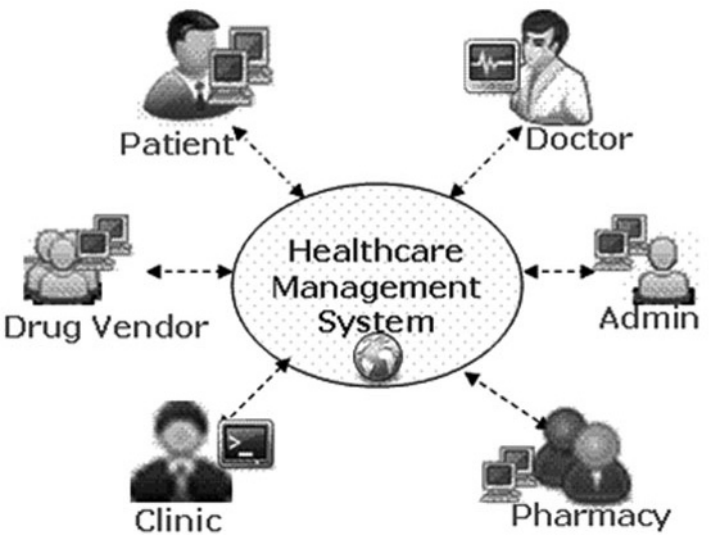

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