The Child and Newborn

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Editorial

There are three basic indications of antimicrobial use: for treating infections, empirical use and for prophylaxis. In ideal circumstances, antimicrobials should be used only in case of proven infections. Hence proper diagnosis is the first step towards rational antimicrobial use. Empirical use is subjective, where it is used mainly by personal experience and intuition. Though this is not the ideal way to use an antibiotic but it is the most common mode of antibiotic use. Prophylactic use is indicated only in certain selective situations where standard protocols have to be followed. Unnecessary use of antibiotics results in destruction of susceptible bacteria and selective proliferation of resistant strain leading to bacterial drug resistance.

Indications of antibiotic therapy

Antibiotics are used under various situations.

Definitive therapy:

Antibiotic used in cases of proven bacterial infection. Effort should be made to confirm and do susceptibility test. Based on the report narrowest effective antibiotic should be used.

Empirical therapy:

Here the choice of antibiotic depends upon the most likely pathogen in that particular anatomical site and the likely sensitivity pattern. Empirical therapy is given in life threatening infections where appropriate sample should be collected prior to initiating treatment. Initially broad spectrum antibiotic or combinations are used followed by narrower spectrum when sensitivity results are available.

In less severe community acquired infections antibiotics are prescribed without obtaining cultures. Failure of response or recurrence in such situation is an indication for subsequent culture studies.

Prophylactic therapy:

It is indicated only in certain selective situations where standard protocols have to be followed. The antibiotic used should be narrow spectrum, directed against specific pathogen and used for a short duration. In neonates prophylactic antibiotics are used to prevent ophthalmic neonatorum and group B streptococcal infection. It is also indicated in certain diseases like rheumatic fever, infective endocarditis, urinary tract infection and recurrent otitis media. Post-exposure prophylaxis is used in tuberculosis, malaria, pertussis, meningococcal infection, diphtheria, varicella and influenza. Other indications are asplenia, human and animal bites and surgical prophylaxis.

Combination antibiotic

A single antibiotic with narrow spectrum helps in maintaining the normal bacterial flora, reduces cost and prevents adverse effects but there are certain situations which merits use of combination antibiotics.

Prevention of resistant strains:

Sometimes mutations occur in genes encoding for resistance in certain bacteria. Treatment with a single antibiotic in certain infections kills the sensitive strain and help to select the resistant strain. Examples are rifampicin for Staphylococci and imipenem for Pseudomonas. Addition of a second antibiotic with a different mode of action like aminoglycoside to imipenem in systemic pseudomonas infection might be helpful.

Synergistic or additive activity:

Combination of third generation cephalosporin with an aminoglycoside are examples of synergistic or additive activity for Enterococci, *Streptococci viridans* and *P. aeruginosa.*

Polymicrobial infections:

Certain situations like intra abdominal infections, brain abscesses and fever in neutropenic patients the chances of a mixed infection with multiple pathogens is high. Combination antibiotics are indicated in these situations with various combinations.

Reduction of adverse effects:

Antibiotics with low safety may be combined in lower doses provided they are synergistic to reduce adverse effects of the individual antibiotic. Combination of streptomycin with enicillin in subacute bacterial endocarditis caused by *S. faecalis* is one such indication.

Due to various reasons children are more vulnerable to infections. It is quite obvious that antimicrobials are one of the most frequently prescribed components of any pediatric prescription. As we have limited stock of antimicrobials in our armamentarium, it must be used judiciously. It is imperative that antimicrobial resistance is a direct consequence of antimicrobial use. In spite of advocacy both continue to escalate. The situation is often complex in practical field as it is not easy to confirm the presence of an infection. But if few principles are followed, it can be used rationally. This will prevent antimicrobial misuse and in the long run there will be less resistance. Antimicrobial resistance is a cause of great concern because detection of even a single instance of antimicrobial resistance is a microcosm of a larger perspective. Microbes are ubiquitous in nature. They cannot be confined by geographical, social or man made boundaries. It is quite obvious that we share a single global ecosystem in terms of antimicrobial resistance too.

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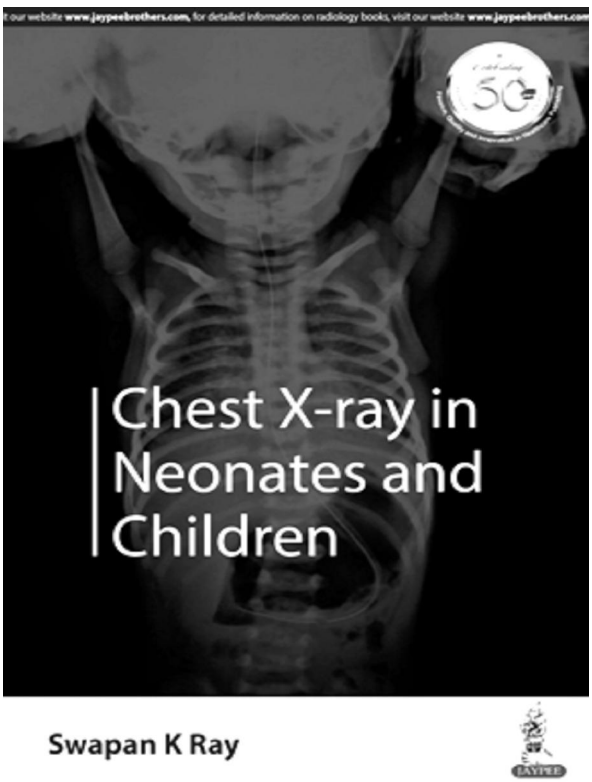

About the book

As medical science develops around us at an astounding pace, it has become more pertinent than ever to integrate indispensible clinical skills and practices with best available investigative backup to provide optimal care to our patients. Along with conscientious bedside examination, use of precise and patient-oriented diagnostic workup has become the standard of care. Radio-imaging forms an important tool in this rapidly expanding arsenal. Despite a wide array of sophisticated imaging technique now in use, Chest X-ray still remains the most easily available and readily used imaging technique in wider medical field in general and pediatrics specifically.

While a thorough training in this speciality is irreplaceable, development of basic skills in reading Chest X-rays can provide timely and accurate management to at risk patients. In this context this books fills a glaring lacunae. The book provides a lucid and stepwise guide to glean clinically relevant information from a skiagram necessary for everyday clinics with focus on ensuring that important findings are not missed. Its pocket friendly size holds out an instant attraction for students wishing for a quick grasp of concepts and fearful of ponderous tomes. Practicing doctors wishing to renew acquaintance with the subject will find it more than adequate. Beguiling readers with its lack of volume, it does not lack in substance. It covers a wide field with a separate section for neonatal chest X-ray. Replete with excellent quality pictures which are sine qua non to understanding radio-imaging, it also provides essential clinical snippets and explains each scenario with pointers to aid easy diagnosis. I expect that more than a few readers will be grateful to the book for deftly covering the subject in a concise yet comprehensive manner. I wish the author my best regards for this brilliant work and hope that the book will find its well deserved place in students' bookshelves and doctors' apron pocket.

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A Critique on Cough Cold Medicines

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Introduction

Cough and cold are common presenting symptoms in pediatric outdoor practice. More often than not these are symptoms of viral infections. Such episodes of viral infections are self limiting and require symptomatic relief. However the basic dilemma is to decide what constitutes symptomatic relief? Do we have the right preparations to treat these symptoms? Are we over using irrational combinations flooding Indian pharmaceutical market? Are we missing out on side effects of such preparations simply because we do not have any Adverse Drug Reaction (ADR) monitoring system in place?

Following is an attempt to answer some of these baffling questions.

What is the ground reality? Do we know what we prescribe?

The author has interacted with several child care health providers about use of CCM(Cough Cold Medicines). When one asks the audience collectively about viral URTI, they all agree that the condition is self limiting. When we further probe about use of CCM almost all agree that they use them frequently. When a list of numerous CCMs is put up all of them would say affirmatively that they know about these preparations and that they use them. However the catch comes when we ask to give details of the ingredients of these preparations. Most of them are off the mark regarding the actual ingredients and their dosage. The fact is we are bombarded with several preparations with multiple ingredients about which we know little but tend to use often.

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What are the issues with CCMs?

The challenges are two fold.

A. Issues of general nature.

B. The scientific scrutiny.

General issues

1. Combinations with several ingredients do not stand the scientific scrutiny of rationality of Fixed Drug Combinations (FDCs). FDCs by nature suffer from several limitations like differing dosages, dosage schedules, inability to pin point ADRs and unnecessary consumption of non indicated medicine. The rationale for FDCs is synergistic action, ease of administration, probable cost saving and in case of antimicrobials to reduce drug resistance.
2. The physician cannot remember exact contents of even a few of them.
3. Parents often over dose the children as these are generally sold as OTC preparations.
4. The trade names are often confusing. Various preparations are available with same trade name with minor variations in the name but significant difference in the contents. Drops, syrups, expectorants are some of the examples of these confusing brand name scenario.

Scientific scrutiny

1. Efficacy:

The foremost issue is whether the various agents used in CCMs are really effective in relieving the symptoms of common cold? Many studies have found that these agents are really not having significant effects on the symptoms for which they are administered.

2. Safety:

Are these agents safe for use in children? Most of these agents have not been studied in children and data are extrapolated to children. Same is true for dosage of these agents. Hence over years the scientific community has realized that these agents are not safe enough for young children. A significant mortality is reported in relation to use of CCms in children.

The science of CCMs

The main ingredients of CCMs are

A. Decongestants

B. Antihistamines

C. Cough Suppressants (antitussives)

D. Mucolytic agents

E. Paracetamol

F. Bronchodilators

Decongestants:

(i) Phenylephrine is a common ingredient of CCMs. It is an α-adrenergic agent with decongestant effects. Stimulation of α1-adrenergic receptors on post capillary venules and of α2-adrenergic receptors on precapillary arterioles leads to vasoconstriction, resulting in a reduction in nasal congestion. Though found effective in adults, studies in children have not supported its use. The common side effects are excitability, headache, nervousness, palpitations, tachycardia, arrhythmias, hypertension, nausea, vomiting, and urinary retention.

(ii) Topical decongestants are effective for few hours but overuse can lead to rhinitis medicamentosa with severe rebound congestion.

Antihistamines:

Antihistamines are not recommended for viral common cold. They are recommended for allergic rhinitis which is characterized by paroxysmal sneezing, nasal itching, running nose and nose block. Fever is usually not an accompanying feature. In management of allergic rhinitis second generation antihistamines are recommended. Most CCMs have first generation antihistamines with common side effects like sedation, cognitive dysfunction and irritability.They can thicken the secretions. There are reports indicating deteriorating scholastic performance in children who are frequently administered these preparations.

Antitussives:

Coughing is a natural mechanism to clear airways of secretions and keep them patent. However it is one of the most bothersome symptoms for parents. Antitussives can be harmful in children who have secretions in the airways. However they may be useful for suppressing dry irritating cough.

Dextrometharphan and Codeine are the commonly used cough suppressants.

Dextrometharphan is a centrally acting narcotic analog (D-isomer of codeine analog). It is relatively well tolerated. Few studies in children have not shown it to be more effective than placebo. Accidental over ingestion can cause serious CNS side effects and death. AAP (American Academy of Pediatrics) does not recommend its use. In recent years drug abuse by adolescents in USA has been reported. It causes mild intoxication, euphoria and stimulation. Even deaths have been reported in young adults. It has a potential for abuse because of cheap availability and a general belief that it is harmless.

Codeine is a centrally acting narcotic drug. Studies in children do not show efficacy. It has serious side effects like sedation, constipation, nausea, vomiting and dizziness. With over ingestion, it can cause CNS depression.AAP does not recommend its use in common cold and cough.

Levocloperastineis a new entrant in the field of antitussives. It has both central and peripheral action (antihistaminic, antiserotonergic and smooth muscle relaxant). It does not cause sedation and has no potential for developing dependence. It has efficacy similar to codeine. Though well tolerated, it can have some side effects like vomiting, anorexia, somnolence and headache.

Mucolytic agents :

They do not have a role to play in routine management of URTI and LRTIs. They have been recommended for conditions like cystic fibrosis in large doses.

Antipyretics need to be administered for the purpose of giving some comfort to the child and should be

used on 'as and when required' basis. There is no rationale for combining them with other ingredients of CCMs and giving them round the clock. Such practices can mask clinical condition like a serious bacterial infection.

Bronchodilators are recommended for children with asthma or reactive airways. They should not be combined with antitussives and antihistamines.

What is the evidence : The Conclusions

(a) Allergic rhinitis should be treated with second generation antihistamines

(b) Nocturnal spasmodic cough may indicate bronchospasm and should be treated with bronchodilators.

(c) Dry irritating cough may be treated with antitussives with single ingredient preparations.

(d) Many studies have reported ineffectiveness of CCMs in management of common cold in children below 6 years age.

(e) Published literature states that CCMs should not be used below 2 years of age.

(f) FDA recommends that symptomatic oral over-the-counter (OTC) therapies (often containing antihistamines, antitussives, and decongestants) should not be used for infants and children <2 yr of age. FDA Advisory committee has voted to ban them for use below 6 years. In the USA manufacturers' label reads "not to be used below 4 years".

(g) AAP also recommends not using OTC CCMs in children less than 6 years age.

(h) The currently available CCMs are irrational multi-drug combinations and have a huge potential for side effects.

(i) Pediatricians and parents need to accept the fact that effective treatment for common cold remains elusive

(j) We need to educate the parents that it is a self limiting illness and medicines can do more harm than good.

Further reading:

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Hereditory Angioedema – An Overview

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Introduction

Hereditory angioedema is a disorder characterized by repeated and transient attacks of subcutaneous and/ or mucosal edema leading to angioedema of the extremeties, face, upper airways and the gastro intestinal tract[1].

Hereditory angioedema(HAE) was first described by Sir William Osler in 1888, and ever since our knowledge about the disease is expanding.

The condition is mostly seen in families and is transmitted as autosomal dominant trait. It is a debilitating disease which can be life threatening at times. Though about 10-20% of the world population suffer an attack of angioedema or urticaria at some point of time during their lifetime, the prevalance of HAE is estimated to be 1 in 100,000 and involves almost all races[2,3]. Females are more prone than males. The reason for discussion about this rare disease entity is to emphasise the fact that prompt detection and treatment can significantly improve the outcome in life threatening situations, and can help to avoid unnecessary surgical procedures.

Pathophysiology[3-7]

The basic defect in the affected individuals is the inability to synthesise normal levels of functional C1inhibitor (C1-INH)of the complement system.C1INH is encoded by a gene on the long arm of chromosome 11.

Normally C1-esterase INH suppresses the action of proteases C1r and C1s thereby inhibiting the cleavage of C2 and C4.

When C1INH is deficient or dysfunctional C1INH is produced in large quantity and the C 4 levels are reduced below the lower normal limit both during and in between attacks. Besides inhibiting C1, C1 INH is also a major inhibitor of Kallikrine. So diminished levels of C1 INH or dysfunctional C1INH lead to unregulated activation of Classical Complement pathway and increase in Kallikrine production even with mild trauma. Kallikrine in its turn cleaves plasma kininogen to produce bradykinines which is the major mediator of angioedema.

C1-INH also supprsses MASP-2 (Mannose binding lecting Associated Serine Protease)of Lectine pathway and Factors XIa and XIIa of the Clotting system.

This is a normal control mechanism of the Complement system without which the unhindered consumption of complement components would cause severe damage to the host.

When C1-INH is absent or dysfunctional the uncontrolled C1 and Kallikrein activity lead to cleavage of C4 and C2 with release of bradykinine.

Bradykinine produces vasodilation and localized nonpitting oedema or angioedema.Depending on the C1-INH status HAE is classified into 3 types.

(i) Type I HAE : Reduction in synthesis of C1-INH (80% of cases)

(ii) Type II HAE : Synthesis of dysfunctional C1-INH (15%of cases)

(iii) Type III HAE : With normal level of functional C1-INH. This has been described as recently as 2000 and studies point towards some correlation with estrogen levels of the patient.

Clinical features[4,5]

The initial attacks are usually encountered between the age of 1yr and 5 years. They become severe in late childhood and adolescence. But in some cases first symptoms occur in adult life.

Females are more prone than males.

Usually the attacks are preceded by a history of trauma or invasive procedure like tooth extruction, rigorous exercise, menstrual periods, fever or

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emotional stress. Even tight fitting dress, cold exposure have been reported to have precipitated the symptoms. A strong family history is often present.

But TypeIII HAE may occur sporadically.

The attacks are typically recurrent and consists of "angioedema" or localized nonpruritic swelling involoving all the layers of the skin or the walls of hollow viscera.such as the respiratory system and the GI tract.

There is non pitting, non pruritic oedema of the skin with swelling of the lips, extrmeties and genitalia.

Breathing distress and choking may occur due to involvement of the larynx (laryngeal oedema).

Involvement of GI tract manifest as swelling of the tongue , abdominal pain of varying intensity, features of obstruction or nausea vomiting and diarrhea.

Abdominal pain may present with acute onset leading to unnecessary surgical procedures or it may present as chronic recurring type.

Children often present with features of acute abdomen without respiratory and dermatological symptoms thereby making the diagnosis difficult.

As secondary reduction of C4 often predisposes SLE. HAE and SLE may present as comorbodities posing difficulty for diagnosis of the former[3]. It will be worthwhile to remember that bradykinine mediated angioedema of HAE is refractory to treatment with corticosteroids and antihistamines.

Drugs like ACE inhibitors worsen the disease process by inhibiting the degradation of bradykine.

TypeIII HAE has some correlation with the hormone estrogen as in females menstual periods. Intake of oral contraceptive pills appear to precipitate the condition.

Diagnosis

The striking clinical presentation of HAE should alert the physician.

There is no specific laboratory test for HAE.

C1-INH level is low in type I HAE but is normal type II and type III HAE.

C3 and C4 levels are low in both type I and type II HAE but normal in type III.

Treatment

Treatment of HAE consists of :-

(i) Treatment of an acute attack.

(ii) Prophylaxis.

Treatment of acute attack :

Infusion of CI-INH. In 2009 purified CIINH, Berinert has been approved for treatment of acute attacks in a dose of 20 units/kg given IV[8].

Alternate agents recommended are Icabitant (selective competitive antagonist of Bradykine ß2 receptor) or Ecallantide (Kallikrine inhibitor) FDA approved the use of Ecllantide in adolescents 16yrs or older. In rare cases Ecallantide can cause anaphylaxis[4,9,10].

As all the three above mentioned agents are not available in India yet, our only reasonable choice remains infusion of fresh frozen plasma (FFP). FFP is useful in replacing CI-INH levels. Very rarely the angioedema can worsen due to the complement factors present in FFP[11].

Prophylaxis :

Human plasma derived, purified CIINH is approved for use in adolescents and older for prophylaxis. As the half life of this product is about 40 hrs, the approved regimen is 1000 U given twice a week. But this is not available in India.

Other options are attenuated androgens like Danazol and antifibrinlytes like Tranexamic.acid.

But attenuated.androgens should be used in children with caution for their side effects like premature closure of epiphyses, virilization on long term use[12].

Conclusion

Hereditory angioedema is a rare disorder, transmitted as autosomal dominant trait and characterized by repeated and transient attacks of angioedema often with serious consequances.

The basic defect is the inability to synthesize normal levels of functional C1 esterase inhibitors in affected individuals, leading to unhindered activity of bradykinine. Clinical feature characteristically consists of reccurrent attacks of non-pitting,non-pruritic angioedema involving lips and,tongue and extrmetes, breathing distress and abdominal pain. Laryngeal edema is the most dreaded manifestation. As this angioedema is caused by bradykinine it is refractory to antihistamines and corticosteroids.

Timely diagnosis and prompt management can avert life threatening consequences and unnecessary sergical procedures.

Non pitting, non pruritic angioedema should raise suspiscious of HAE.

Plasma derived purified C1-INH is the main stayof the treatment.

Icabitant (selective competitive antagonist of bradykine ß2 receptor) and Ecallantide(Kallikine inhibitor) are other two options.

As none of the three are availbale in India. Fresh frozen plasma (FFP)is the only reasonable choice.

Attenueted androgens like Danazol are recommended for prophylaxis. But these should be used with caution in children due to their serious side effects.

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A Case Series of Severe Pallor-congenital Leukemia in Neonate

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Abstract: *3 neonates presented in early gestational period with severe pallor along with other associated features.Complete blood count with peripheral smear examination showed abnormal cells suggestive of Congenital Leukemia.Bone marrow examination confirmed the diagnosis. All patients needed blood transfusion.However,Immunohistochemistry and Cytogenetic study could not be done due to paucity of investigation in our institute and patients were referred to higher centre.*

Key Words:*Neonates, Pallor, Leukemia*

Case 1

The girl baby (27 day old) born out of of an uneventful pregnancy,G1P0 with no history of consanguinity, normal vaginal delivery,birth weight 2.9kg presented with refusal to suck and gradual swelling of abdomen for last 15 days,fever for last 10 days.On clinical examination,vitals were stable with no features of shock.Baby had severe pallor with multiple purpuric spots and red nodules (Leukemia cutis) over skin (Fig 1). Spleen was palpable 5cm below costal margin.CBC showed marked leukocytosis over 1 lakh (110000/cmm), low platelet count(35,000/cmm) and reduced hemoglobin(6 gm%) and atypical cells.LFT showed conjugated hyper bilirubinemia(total serum bilirubin 13.12mg/dl, conjugated 8.5 mg/dl).Torch screen was negative .USG whole abdomen showed splenomegaly(9.2cm) with mild ascites.Bone marrow biopsy showed immature myeloid cells (meta, myelo promyelocytes) 48% and Blast cells-30% (Fig 2).

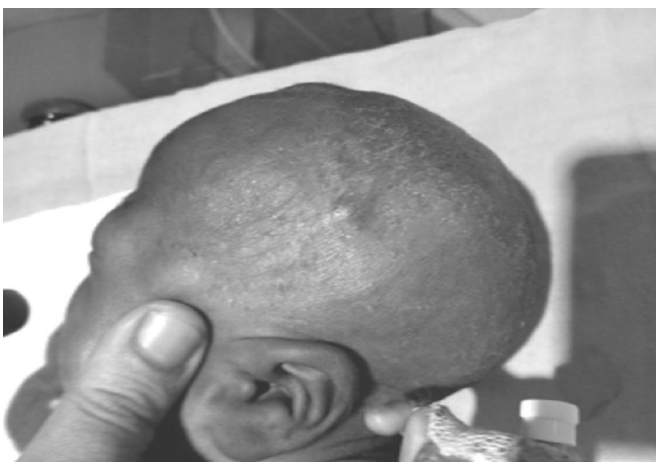

Fig 1-Leukemia Cutis

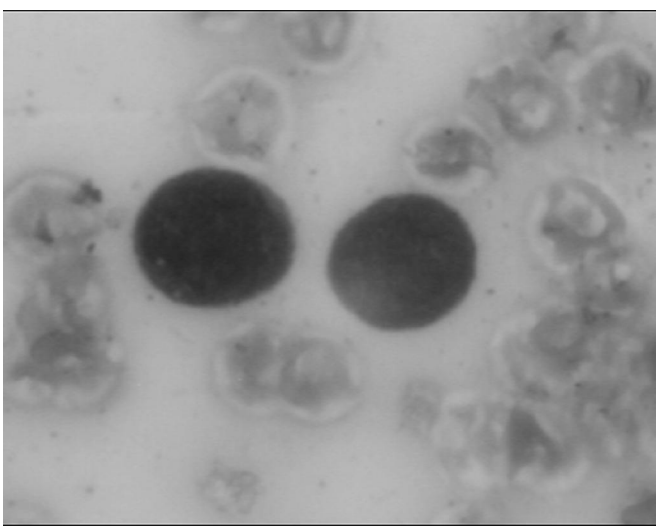

Fig-2-Bone Marrow Biopsy showing Blast Cells

Case 2

36 wks, preterm, small for gestational age baby, born out of non-consanguinous marriage,delivered by Caesarian Section due to premature rupture of membrane,birth weight 1.9kg, presented with lethargy and paleness since birth. On physical examination at day 7 of life,skin had multiple purpuric

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spots.Vitals were stable.Baby had occasional episodes of hypoglycemia with liver palpable 4cm below costal margin. CBC showed decreased leukocyte count(2000/cmm), low platelet count (10,000/cmm) and reduced hemoglobin (6 gm%) and atypical mononuclear cells 26%.Band cells 4%. LFT showed conjugated hyper bilirubinemia (total serum bilirubin 10.23mg/dl, conjugated 7.5 mg/dl). Torch screen negative.USG whole abdomen showed significant ascites with hepatomegaly. Urine for AFB detection RNA PCR was Negative. Bone marrow biopsy showed Blast cells in increased number constituting about 25% of the marrow nucleated cell population. These blast cells are largely pleomorphic having dispersed chromatin, mainly of myeloid origin, suggestive of acute leukemia(Fig 3).

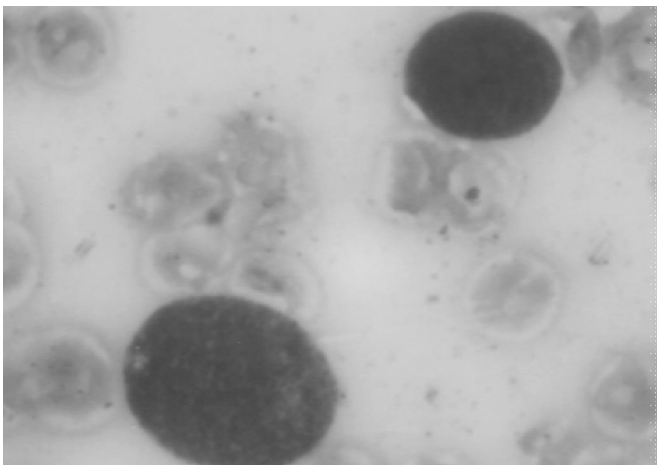

Fig 3. Oil immersion of Bone Marrow Biopsy

Case 3

Term, appropiate for gestatational age boy baby, born from an uncomplicated normal vaginal delivery presented on day 27 of life with multiple echymosis (fig 4) and red nodules (fig 5) all over the body. Patient was apparently well 7 days back and gave no history of fever. On physical examination patient had severe palor. Head to foot examination revealed mongoloid slant of eves, sandle foot gap and simian crease.vitals were stable and patient was feeding well.Liver was palpable 5 cm below costal margin and spleen was palpable 4cm below costal margin.CBC showed marked leukocytosis(64000/cumm) ,low platelet count (45,000) and reduced hemoglobin (5gm%). Peripheral smear examina-tion showed marked immature myeloid cells and myeloblasts (74%). RBC was normocytic, normochromic. Bone marrow aspiration from tibial tuberosity showed hypercellular marrow with myeloid maturation shift to the left with increased myeloblast constituiting about 30% of the marrow non erythropoid cell population. Megakaryocytes and erythropoiesis were markedly depressed. LFT showed conjugated hyper bilirubinemia. TORCH screen and blood culture were negative.Karyotyping showed triple trisomy 21(fig 6).

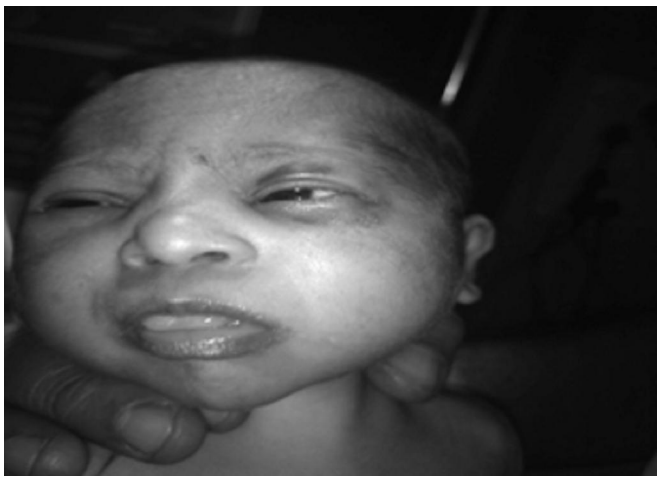

Fig 4 Ecchymosis over left eyelid

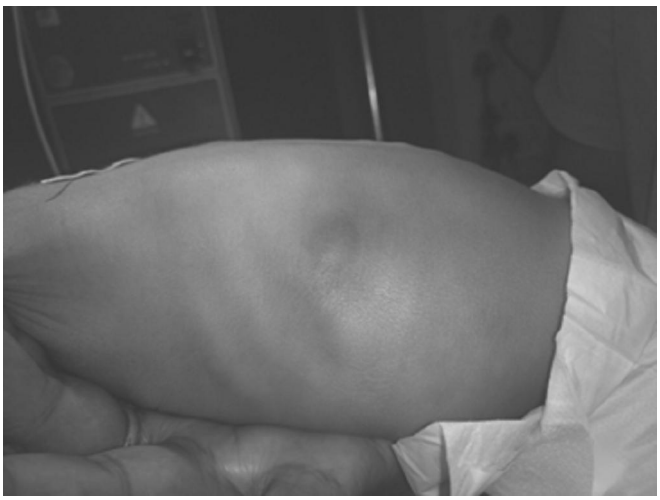

Fig 5 Red nodules on back

Management

All the three cases were initially thought to be late onset sepsis and were managed with IV fluids and antibiotics. Blood transfusion was given. TORCH screening and blood culture were sent for all three patients which came to be negative.There was no improvement in blood picture after repeated transfusions.The counts showed pancytopenia in one patient with leucocytosis in the other two. Peripheral blood examination showed abnormal Cells in all three patients and bone marrow

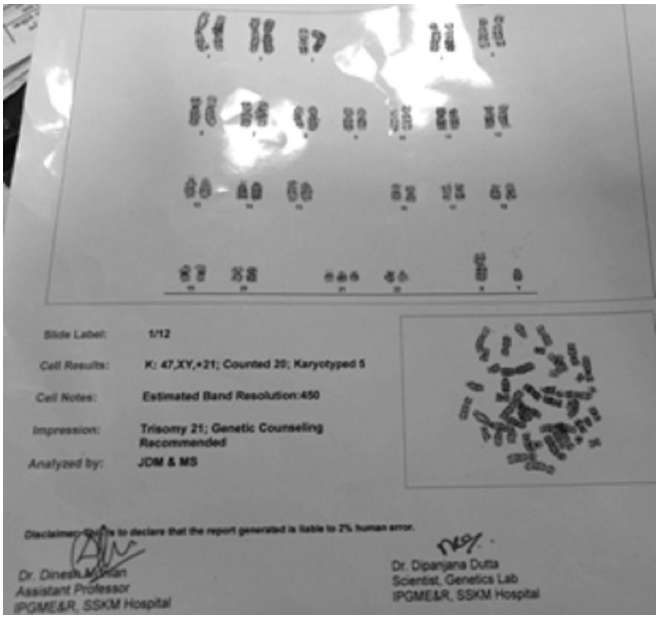

Fig 6. Karyotyping showing trisomy 21

examination confirmed the diagnosis. Patients were referred to pediatric hematology centre for further management.

Discussion

Congenital leukemia (CL) is luckily a very rare hematologic malignancy that originate in utero and usually get diagnosed from birth to 6 weeks of life. Usually average time of diagnosis of congenital leukemia is from birth to six weeks of life. Although the etiology is unknown, the presence of leukemia at birth suggests genetic abnormalities and possibly intrauterine exposures to drugs or other toxins as contributing factors[1,2].

The criteria for diagnosis are:

(a) Disease presentation at or shortly after birth (within 30 days of birth).

(b) Proliferation of immature/ precursor white cell population.

(c) Infiltration of cells into extra-hemopoietic tissues

(d) Absence of congenital leukemia simulators[3,4].

Congenital leukemia (CL) simulators include TORCH infection, Congenital HIV Infection, Hemolytic disease of the newborn (ABO or Rh incompatibility), hereditary spherocytosis, twin-twin transfusion,other neoplastic infiltrates (metastatic neuroblastoma, rhabdomyosarcoma, Langerhans cell histiocytosis). Neonatal or congenital leukemias are generally myeloid in origin unlike childhood leukemia which are lymphoid in origin.Neonatal leukemia is more likely to present with poor prognostic factors.Neonatal ALL has a disease-free survival rate of ~10% compared to >70% in older children[5] .Neonatal leukemia is the leading cause of death in neonate due to neoplastic disease. There is high index of suspicion in cases of Down syndrome and hydrops fetalis. Essential karyotyping in such individuals antenatally by collecting fetal cells through amniocentesis or cordocentesis should be done for cytogenetic study and demostration of blast forms[6,7].

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Enteric Fever Presenting as Acute Pancreatitis: A Case Report

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Abstract : *Enteric fever is very common in developing countries like India but Acute Pancreatitis as a complication of Enteric fever is rare. We report the case of a 7 year old child admitted to our hospital with complaints of fever and pain abdomen and was diagnosed to be a case of Acute Pancreatitis but was later found to harbour Salmonella typhi and hence was diagnosed to be a case of Enteric fever complicated with Acute Pancreatitis. So in any patient presenting with fever and pain abdomen, this rare association should be kept in mind especially in endemic areas like our country.*

Keywords: *Enteric fever, Acute Pancreatitis, Fever, Abdominal pain*

Introduction

Enteric fever is caused by *Salmonella typhi* and remains a serious health threat in the developing world[1]. It involves various organs especially the gastrointestinal system leading to complications like intestinal hemorrhage and perforation, acute cholecystitis, acute pancreatitis and hepatitis[2]. Enteric fever presenting as a acute pancreatitis is rare[3] but needs to be kept in mind while dealing with a case of fever with abdominal pain in an endemic country like India.

Case report

A 7 years old male child was admitted to our hospital with chief complaints of fever for 15 days, loose stools for 6 days and abdominal pain for 1 day. The fever was high grade and continuous with no history of cough, rhinitis, difficulty in breathing or urinary symptoms, associated with 5 to 10 episodes of greenish loose stools for last 6 days and pain in the abdomen with occasional radiation to the back. The child was admitted to our hospital two days back but the parents took the child to a private hospital against our advice and again due to financial crisis brought the child back to our hospital within two days.

On examination, the child was extremely sick looking, drowsy, disoriented and irritable to touch with a pulse rate of 102/min, respiratory rate of 35/min and oxygen saturation on pulse oximetry of 94-96% with moist oxygen via mask. The axillary temperature was 102.8^{0}F and there was a nasogastric tube in situ with bilious secretions in the bag. Further the abdomen was tense, distended and diffusely tender with no palpable mass, shifting dullness couldn't be eliciteddue to abdominal tenderness. Other systemic examinations were within normal limits. The child had undergone certain investigations prior to admission whose reports were available that said, serum amylase was 462 IU/L, serum lipase was 229 IU/L, TLC was 2600/cmm, TPC was 55,000/cmm and ultrasonography of the abdomen reported hepatomegaly, splenomegaly, slightly bulky pancreas with prominent pancreatic duct and moderate ascites. Other reports were within the normal range and hence in the setting of the above findings, a provisional diagnosis of acute pancreatitis was made and the child was managed accordingly with fluids and antibiotics.

The investigations done in our hospital revealed a corroborative picture, with TLC being 3,500/cmm, TPC being 1 lac/cmm, serum triglycerides being 209 mg/dl and chest X ray (PA view) showing bilateral pleural effusion. Ultrasonography of abdomen revealed that the tail of pancreas was bulky and heterogenous and there was ascites. To confirm our diagnosis CECT Abdomen was done which clearly stated that the pancreas was bulky with non-enhancing head and neck regions with moderate

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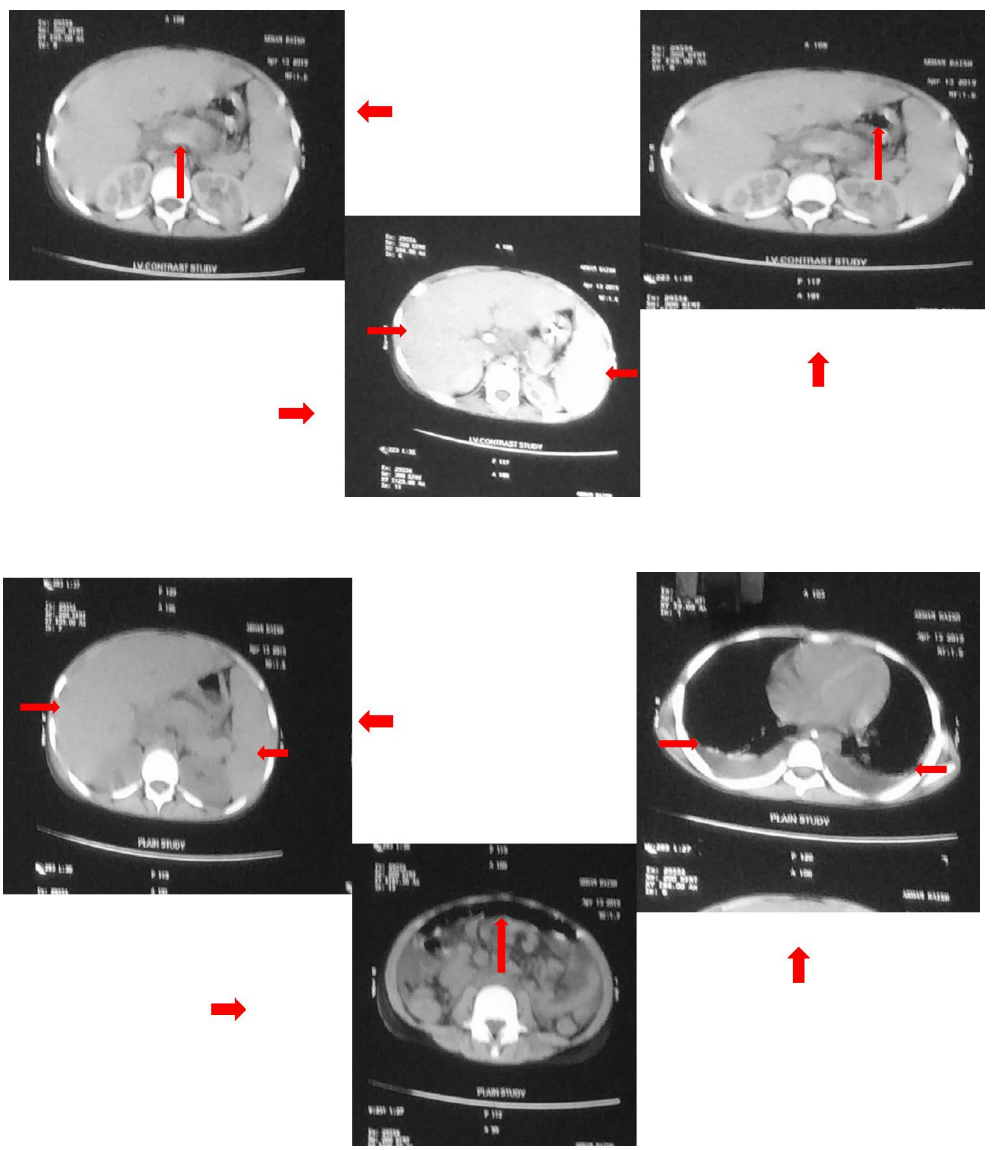
ascites, bilateral pleural effusion, hepatomegaly and an acute pancreatitis modified CT severity index of 6/10.

But to our surprise, as the child was investigated for fever, it was seen that the Widal test was positive with the titre of both TO and TH antigens positive upto 1/160. The picture then became clear in our mind that this was a case of Enteric fever complicated with acute pancreatitis. As per the change in our diagnosis, our management plan also changed and the child was started on Injection Ceftriaxone (1gm) IV twice daily. The child had altered blood in the stool for which a Pediatric Surgery opinion was sought. The Pediatric Surgeon opined it to be a case of bleeding from typhoid ulcers in the intestine and advised to continue conservative management. To firmly establish the diagnosis of Enteric fever, the blood culture report was positive for *Salmonella typhi* and hence we were convinced that it was a case of Enteric fever complicated with Acute Pancreatitis.

A dramatic improvement in the status of the patient was seen after initiation of appropriate antibiotics. Fever subsided within four days, oral feeding was initiated, abdominal pain, tenderness, ascites and pleural effusion disappeared in a week, bowel and bladder movements were normalized and finally the patient was discharged after two weeks.

Discussion

The causes of abdominal pain in a patient with Enteric fever may be intestinal haemorrhage and perforation, acute cholecystitis, hepatitis, hepatic abscess,



splenic rupture and acute pancreatitis[2,4]. Pathogenic bacteria causing sporadic cases of Acute Pancreatitis are *Salmonella typhi, Yersinia enterocolitica, Yersinia pseudotuberculosis, Campylobacter jejuni, Brucella, Legionella, Nocardia*[5]. Salmonella infection can cause Acute Pancreatitis but it is an uncommon presentation in our part of the world[6]. Salmonella infection causes hyperamylasemia in 50% and clinical pancreatitis in 28-62% of the patients as reported in various studies[7]. The exact pathogenesis of Pancreatitis in Salmonella infection is not exactly known and requires further studies. Direct localization of bacteria in pancreas, toxin induced or immune mediated pancreatitis are possible mechanism.[8] Theoretically, we may say that hematogenous or lymphatic or transmural migration via biliary duct system or from duodenum via the main pancreatic duct may occur. Bacteremia due to S. choleraesuis is a usual cause of localized pancreatic Salmonella infection but other causes may be gastroeneteritis by *S. typhimurium* and Enteric fever by *S. typhi*[8]. Pancreatitis due to Enteric fever doesn't respond to the usual conservative management but needs specific antimicrobial treatment in addition to supportive management[9].

Conclusion

In the post antibiotic era, Acute Pancreatitis developing as acomplication of Enteric fever is extremely rare. Nevertheless, it should be kept in mind as differential diagnosis in case of patients presenting with fever and severe abdominal pain. Appropriate antimicrobial therapy can improve the prognosis and prevent life threatening complications.

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Scrub Typhus Associated Hemophagocytic Lymphohistiocytosis (HLH) in Early Infancy

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Abstract : *Scrub typhus in early infancy is very rarely reported and unusual. Scrub typhus is known for its varied presentations ranging from mild fever to severe shock. Here we present a case of a male baby 2.5 months old who presented in Emergency in a state of cardiac arrest, resuscitated and later diagnosed as a case of Hemophagocytic Lymphohistiocytosis (HLH) and also tested positive for Scrub Typhus.*

Key Words: *Hemophagocytic Lymphohistiocytosis (HLH), Early infancy, Scrub typhus.*

Introduction

Scrub typhus is an important cause of acute febrile illness in South and East Asia and the Pacific including India. In India infections have been reported from various states and union territories like Maharashtra, Delhi, Karnataka, West Bengal, Pondicherry, Kerala, Tamil Nadu, Himachal Pradesh, Jammu and Kashmir, Rajasthan, Meghalaya, Manipur, Goa and Uttarakhand[1]. The infection is transmitted via chigger (larval mite) bites and involves many antigenically diverse strains of *Orientia tsutsugamushi.* Infection-associated HLH has prominent links with various viral, bacterial, fungal and parasitic infections, including Epstein-Barr virus (EBV), influenza, typhoid, tuberculosis, leishmaniasis and scrub typhus[2]. To date, previous examples of scrub typhus-associated HLH in children have been described only in a case series and lowest reported age is 8 months[3] . No case has been report in early infancy.

Case report

A 2months old male child , from Midnapore (E) was admitted with history of 10 days fever, respiratory distress and with two episodes of convulsion. The baby was brought in emergency department of Medical College Kolkata in a state of cardiac arrest with ECG rhythm showing asystole. The baby was resuscitated and reversal of spontaneous circulation occurred with three cycles of high quality CPR and IV adrenaline.

After resuscitation, heart rate returned but the pulse volume was feeble. So, the baby was shifted to PICU and put on mechanical ventilation and antibiotics and inotropes were started. There were ongoing convulsions which were controlled with phenytoin.

The baby was born at term to primiparous mother with birth weight of 2900 gm. Baby was on exclusive breastfeeding. There was no history of sibling death in the family. On admission, he weighed 4000gm, length and head circumference was 54cm and 37cm, respectively.

Central nervous system examination showed some extension of limbs to stimuli, pupils – B/L normal but sluggishly reacting to light. Gastrointestinal system examination showed hepatosplenomegaly, distended abdomen with sluggish peristaltic sound (Fig 1). Auscultation of chest revealed bilateral course crepetations. There were no skin rash or scar on skin.

In laboratory examination, complete hemogram showed bicytopenia with Hb 7gm/dl, platelet 80,000/cmm, total leucocyte count 16,400 and low ESR 14mm. X-ray chest showing B/L diffuse opacity involving all 4 zones, fulfilling all criteria of ARDS (Fig 2). Total billirubin was 1.7mg/dl, Alanine transaminase and Aspartate transaminases were

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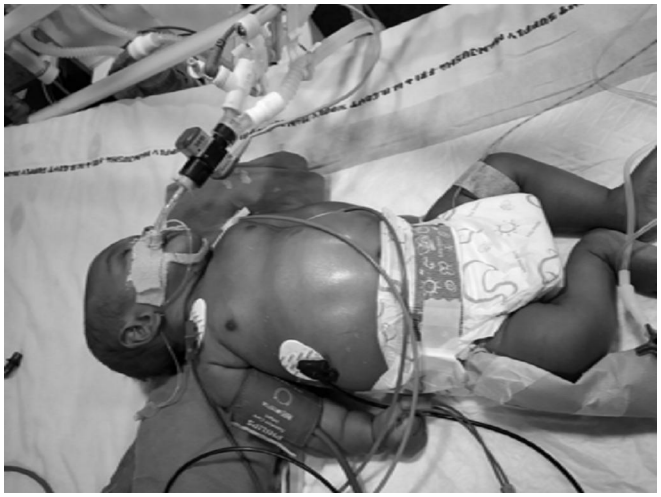

Fig 1. Day 1 showing Distended Abdomen with Edema

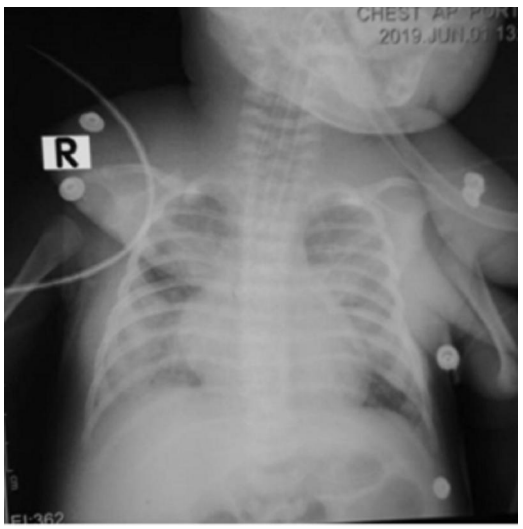

Fig 2. X-ray Chest showing B/L diffuse opacity involving all 4 zones

raised 10 times. International normalization ratio (INR) was 2.4 and aPTT was79.5 sec .The patient had very low Plasma fibrinogen 81 (ref value 272.2) and high Triglycerides 256mg/dl. Serum ferritin report was >40000 ng/ml. A diagnosis of secondary Hemophagocytic Lymphohistiocytosis (HLH) due to sepsis was made as the patient was fulfilling 5 out of 8 diagnostic criteria . IVIg was administered 1gm/kg/day for 2 days. There were no significant improvement after the course of IVIg. On day 3 of PICU admission we got scrub typhus IgM ELISA report, which was highly positive at Optical Density of 4.235. Injection Doxycycline 4.5mg/kg/day in 2 divided doses was given for 14 days along with Methyl Prednisolone pulse doses for 5 days . The baby significantly improved both clinically and hemodynamically, but the course of illness was prolonged due to paralytic ileus and ARDS. Baby was extubated on day 10 and discharged in a stable condition after 17 days. Repeat Serum ferritin after 2 weeks was 699.7ng/ml and peripheral blood picture normalized.

Discussion

Most patients of scrub typhus present with fever for 9–11 days, regional or generalized lymphadenopathy, hepatomegaly with or without splenomegaly, along with abdominal pain, diarrhea and vomiting. A single painless eschar with or without an erythematous rim can be seen at the site of chigger bite[1]. *Orientia tsutsugamushi*, the causative organism of scrub typhus, predominantly infects endothelial cells and causes vasculitis particularly of the lung, heart, brain and kidney[4]. However the organisms also infect macrophages and cardiac myocytes. There is widespread infection of vascular endothelial cells, which corresponds to the distribution of disseminated vasculitic and perivasculitic inflammatory lesions often leading to vascular leakage or hemorrhage as observed in Histopathological examinations.

Patients with severe complications have a reported mortality rate as high as 30% without proper treatment[5]. Recent reports have suggested that the cytokine storm associated with the immune response to *O. tsutsugamushi* infection may be involved in the pathogenesis of complicated scrub typhus[6].

Scrub typhus associated-HLH in children is rarely reported. The formal guidelines for evaluating patients with suspected *O. tsutsugamush*i infection-associated HLH have not been established.

Yingkang Jin, *et al*[3] reported six patients of scrub typhus with sHLH with DIC and ARDS in pediatric age group ranging from 8m – 11yrs who were treated with Azithromycin or Doxycycline of whom 1 did not survive (8m old baby) while the rest went in remission. None of the patients were treated according to 2004 HLH Protocol. All patients were administered intravenous immunoglobulin (IVIG) and mechanical ventilation due to complications related to ARDS, and 5 patients were administered systemic steroid therapy.

Our patient presented at 2 months of age with scrub typhus. There was persistent high grade fever, altered mental changes, bicytopenia, hyper-ferritinemia, hypofibrinogenemia, hypo-albuminemia, hypertriglyceridemia, alongwith hepatospleno-megaly. Patient's clinical course was complicated with ARDS and SHLH. As per the available scientific literature it is the youngest ever reported case. We also treated the patient with Doxycycline , intravenous immunoglobulin (IVIG) and Methyl Prednisolone with very good recovery. Our patient also had severe ARDS required prolonged ventilation. We were not able to perform bone marrow study as the patient was hemodynamically unstable for initially 3 days and as consent was not obtainable from parents.

Conclusion

Though sHLH is rare manifestation of scrub typhus, it should always be kept in mind and relevant investigations should be sent for the same. In this case, Methyl prednisolone and Doxycycline lead to complete recovery. So early diagnosis and initiation of prompt treatment especially on clinical suspicion is the mainstay of management for such patients.

Key messages

Scrub typhus is becoming a very important cause of acute febrile illness in children as more and more cases are being reported and its presentation varies from mild fever with rash to severe sepsis with sHLH (which has a very high mortality rate) as in this case. Therefore scrub typhus has to be excluded in all children with persistent fever.

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A Case of Unilateral Ptosis in Childhood

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Abstract : *A 9 years old girl presented with a history of sudden onset projectile nonbilious vomiting followed by severe headache and gradually progressive ptosis of the left eye 3weeks back. There was no other symptoms apart from on and off projectile vomiting and morning headache. On examination there was left sided occulomotor nerve palsy leading to fixed and dilated pupil and extra-ocular muscle paralysis, those which are supplied by the third nerve. MRI brain with contrast showed a left parasellar SOL compressing over the left internal carotid artery, which showed post-contrast enhancement. The patient was referred to a tertiary centre with neurosurgical management available. A thorough history taking and clinical examination along with investigations have been done to exclude the possible differential diagnoses discussed below.*

Background : *Sudden onset ptosis may indicate a serious underlying disease and needs a careful history, clinical examination and relevant investigations to reach to a definite diagnosis and plan appropriate management and do high risk categorization.*

Introduction

Ptosis is abnormal drooping of the upper eyelid. Normally upper eyelid covers 1/6th of the cornea i.e. 2mm. In ptosis the eyelid covers more than 2mm. Ptosis can be graded into mild (1-2mm), moderate (3-4mm) and severe (>4mm). Levetor muscle function can be graded into good (>8mm), fair (5-7mm) and poor (0-4mm).

Ptosis can be congenital or acquired. Congenital ptosis may be simple or may be associated with blepharophimosis syndrome or Marcus Gunn jaw winking. Acquired ptosis can be neurogenic, myogenic, aponeurotic, mechanical or neurotoxic.

Neurogenic ptosis can be due to third nerve palsy, Horner syndrome, opthalmoplegic migraine, third nerve misdirection, etc.

Myogenic ptosis is due to juvenile myasthenia gravis, myotonic dystrophy, ocular myopathies etc.

Mechanical ptosis is due to pressure effect of any lid tumor or oedema.

Neurotoxic ptosis is usually bilateral, due to envenomation by elapids.

Psudoptosis is apparent ptosis due to inability to elevate the eyelid, caused by blepharophimosis, pthisisbulbi etc.

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Case presentation

A 9 years old girl, resident of a remote village in district South 24 Parganas, was admitted in the pediatric medicine ward with a complaint of on and off projectile nonbilious vomiting, morning headache and gradually increasing drooping of the left upper eyelid for last 3 weeks. There was no history of fever, convulsion, blurred vision or altered sensorium. She did not have any similar complaint in the past. Her birth history, developmental history and family history all were non-significant. On clinical examination, general survery was essentially normal except the ptosis of the left eyelid. Neurological examination showed fixed and dilated left pupil with loss of both direct and consensual light reflex in the left eye. In addition the extraocular muscles supplied by the occulomotor nerve i.e. medial rectus, superior rectus, inferior rectus and inferior oblique were not functioning in the left eye. The right pupil was normally reacting to light, along with normal pupillary light reflex and extraocular muscles. All the other cranial nerves were normal. Motor system was also within normal limits. The cardiovascular, respiratory and gastro-intestinal system were also essentially normal on examination.

Investigations

The patient underwent routine investigations which revealed normal full blood count, urea, creatinine, electrolytes, liver function tests and CRP. Thyroid profile was done which came normal. Tuberculosis was ruled out by doing mantoux test and CBNAAT of sputum, both of which were negative.

An MRI with contrast was done to aid in the diagnosis.it showed a 1cm×1.3cm×1.5cm hypointense lesion in the left parasellar region involving the left cavernous sinus area which was compressing over the internal carotid artery and showed homogeneous enhancement in post contrast study.

Differential diagnosis

This presentation of isolated unilateral ptosis was not so typical because a compressive lesion in the brain parenchyma commonly involves the abducens nerve because of its longest intracranial course. But in this child the abducens nerve was not involved, rather occulomotor nerve was involved.

Common sellar and parasellar mass causing third nerve palsy are meningioma, gliomas, Langerhan cell histiocytosis, pituitary adenoma, cranio-pharyngeoma, leukemia and lymphomas, and metastasis from a primary malignancy.

Discussion over the other differential diagnoses, aneurysm of basilar artery or posterior communicating artery causes unilateral ptosis but there is pupillary sparing because the pupillary constrictor fibres are more superficial which are not compressed by the aneurysm.

Juvenile myasthenia gravis usually presents with bilateral ptosis, but in rare cases it can be unilateral also. There will be a typical history of gradually increasing ptosis and muscle fatigue as the day progresses. It can be detected by doing Tensilon test, acetyl choline receptor antibody assay, single fibre EMG etc.

Thyroid associated opthalmopathy may have associated clinical features of hyperthyroidsm with increased free T3 and T4. But some people may also be euthyroid.

Opthalmoplegic migraine is another differential which presents with typical migraine like headache associated with ptosis, mydriasis and /or diplopia. The patient may have positive family history of migraine.

Horner syndrome usually causes ptosis with pupil constriction. There can be associated anhydrosis and loss of ciliospinal reflex.

Miller-Fischer syndrome and Gullian-Barre syndrome may initially present with ptosis following a preceding illness but there would be associated symmetrical muscle paralysis.

A post-viral sequelae can be ruled out by absence of any fever or cough and cold etc before the onset of ptosis. Besides, if it was a viral infection consequence, it would have gradually improved with time.

Treatmnent

The basic principle of management of a parasellar mass is multimodal therapeutic approach consisting of surgery, radiotherapy, primary or adjuvant chemotherapy and replacement of apparent endocrine deficit if any.

Regular follow-up should be done as there is a high chance of recurrence.

Identification of clinical and radiological features should be done to assess the prognosis and identify the high risk patients.

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Hallermann-Streiff Syndrome: Case Report of A Rare Genetic Disorder

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Abstract: *Hallermann-Streiff Syndrome is a rare genetic disorder that is primarily characterised by craniofacial malformations, hypotrichosis, eye abnormalities, dental defects, degenerative skin changes(Atrophy) particularly in the scalp and nasal regions, and proportionate short stature[1].Majority of patients have a normal life span[2]. Management is symptomatic and genetic counselling should be done.*

Key Words: *Syndrome, Genetic, Rare, Hallermann-Streiff*

Introduction:

Hallermann-StreiffSyndrome was first described in the Medical literature in 1893, which was an incomplete case. Hallermann in 1948 and Streiff in 1950 independently described three cases, recognising this syndrome as a separate clinical entity. Approximately 150 cases have been reported so far in worldwide literature[3].

Case report

A preterm, extremely low birth weight female baby was admitted to NICU. The baby was small for gestational age and was born out of non-consanguinous marriage.Birth weight was 880 gm.The baby had repeated episodes of desaturation in supine posture which reduced in prone positions, though she did not need any kind of respiratory support like CPAP or mechanical ventilation. The followingclinical features were observed:

1. Craniofacial features: Dyscephaly: (occurs in 89-90% of cases)[4].
   a. Frontal and parietal bossing
   b. Wide cranial sutures
   c. Delayed closure of fontanelles
   d. Beaked nose
   e. Hypoplastic mandible
   f. Retrognathia

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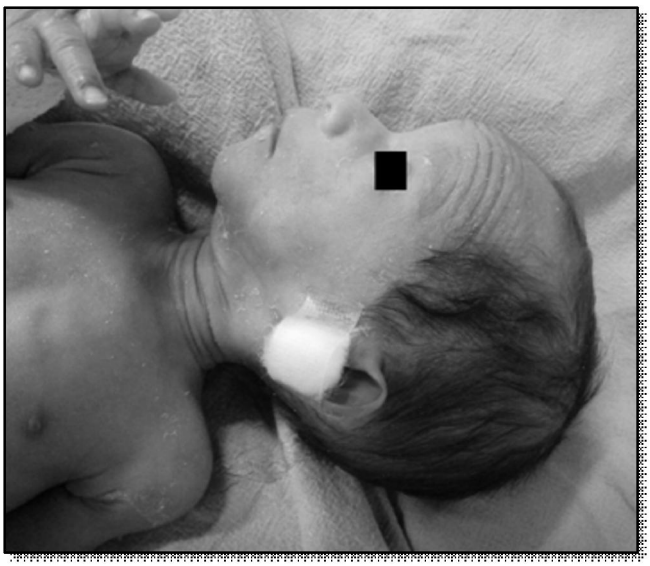

Fig 1. Frontal bossing, beaked nose, retrognathia, hypoplastic mandible

2. Hypotrichosis: (Occurs in 80-82% of cases)
   a. Frontal alopecia
   b. Hypotrichosis (eyebrows and eyelashes are absent)
   c. Brittle and sparse scalp hair
3. Ocular abnormalities:
   a. Blue sclera
4. Mouth
   a. High arched palate
   b. Glossoptosis

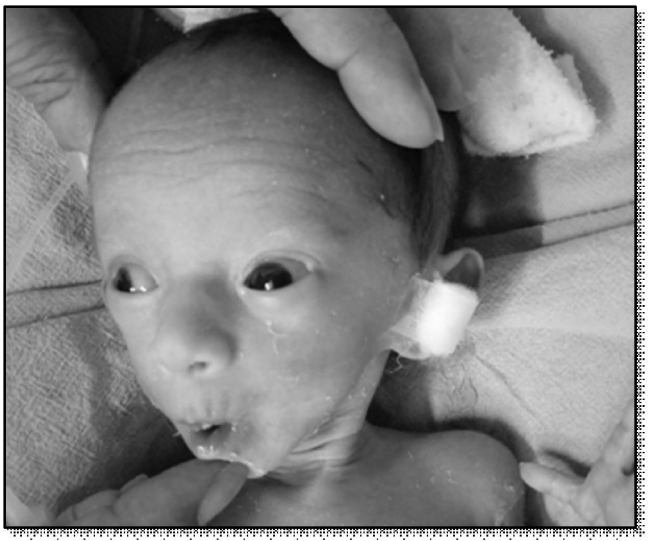

Fig 2. Blue sclera, hypotrichosis, retrognathia

5. Musculoskeletal abnormalities:Absence of Depressor angulioris muscle on right side
6. Ear anomalies: Bat ear on right side

During follow up at 3 months of age, weight was 1.960 kg, length 44 cm and head circumference 32 cm, all <3rd percentile.

Investigations revealed : Hb 8 gm%; WBC count 20,100/cumm; Neutrophils 18%, Lymphocytes 80%, Eosinophil 1%, Monocyte 1%, Basophil 0%; Platelet 4,84,000/cumm; LFT: Total Protein 5.5 g/dl, Albumin 4.1 g/dl, Total bilirubin 0.7 mg/dl, Direct bilirubin 0.3 mg/dl, ALT 18IU/L, AST 68 IU/L, ALP 357 IU/L; Urea 27 mg/dl; Creatinine 0.9 mg/dl; Sodium 138 mmol/l; Potassium 3.4 mmol/l; Calcium 9.3 mg/dl; Phosphate 3.2 mg/dl; Intact Parathyroid Hormone 1.85 pg/ml (9-94pg/ml). TSH 9.4 microIU/ml, FT4 0.6 ng/dl. Echocardiography showed: Situs solitus, AV-VA concordance, IVS intact, PFO seen with L>R shunt, Good biventricular function. Skull X-ray was done at 3 months of age at the time of follow up and consulted with Radiologist who confirmed large skull with poor mineralisation and midfacial hypoplasia consistent with the diagnosis of Hallermann-Streiff Syndrome. Karyotyping was normal. MRI Brain could not be done as the baby could not be sedated for long.

Hence the diagnosis of Hallermann-Streiff Syndrome was made on the basis of clinical features and investigations.

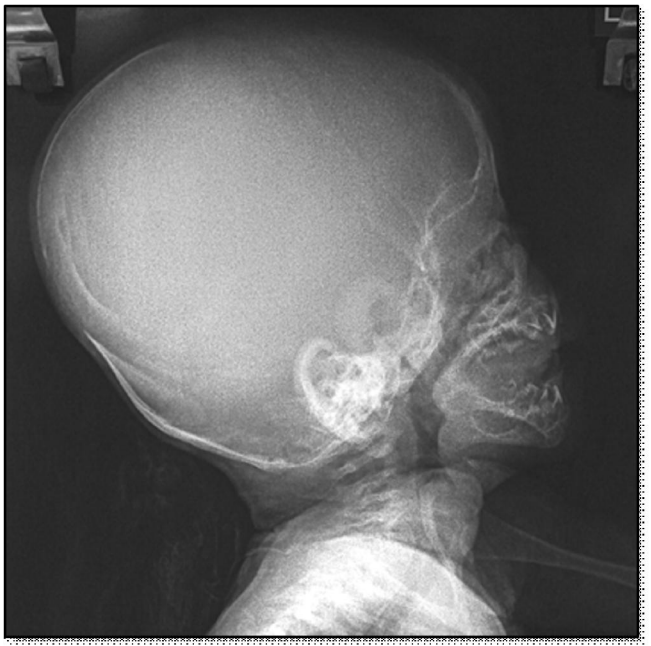

Fig 3. Large skull with poor mineralisation and midfacial hypoplasia

Discussion

The majority of cases of Hallermann-Streiff Syndrome are sporadic, most likely due to a spontaneous de novo mutation in the affected individuals. Few reported autosomal recessive inheritance[5]. It affects males and females in almost equal numbers.

Synonyms of Hallermann-Streiff syndrome:

- Francois Dyscephaly syndrome
- Hallermann-Streiff-Francois syndrome
- Oculomandibulodyscephaly with Hypotrichosis
- Oculomandibulofacial syndrome

In approximately one third of reported cases,infants with HSS are born prematurely and/or have a low birth weight. About two thirds of affected individuals have growth deficiency after birth and associated proportionate short stature.In most cases, children with this disorder have normal intelligence; however intellectual disability have been reported in about 15% of cases.The patient's narrow upper airway along with craniofacial malformation can lead to serious complications, including recurrentrespiratory infections, obstructive sleep apnoea and anaesthetic complications. During early infancy, they may have feeding and respiratory problems. Respiratory infections may contribute to cause of death. A major

difficulty for individuals is visual problems which can lead to blindness despite surgery[6].They can reproduce successfully and bear normal children.

Related disorders are:

- Hutchinson-Gilford Progeria Syndrome
- Wiedemann-Rautenstrauch Syndrome or Neonatal Progeroid syndrome
- Seckel Syndrome
- Osteodysplastic bird-headed dwarfism

Diagnosis

The syndrome may be suspected shortly after birth or during the first year of life by the identification of characteristic physical findings and symptoms. The diagnosis may be confirmed by thorough clinical evaluation, detailed history, and specialised tests (e.g. radiographic, ophthalmologic and dental studies)[5]. No diagnostic cytogenetic characteristics are available[4].

Treatment

There is no cure for this syndrome. Treatment is directed towards the specific symptoms that are apparent in each individuals.There should be periodic ophthalmologic, dental, and ENT check-ups for early detection of complications[7]. Genetic counselling should be done for all affected patients although recurrences have not been reported in siblings or children of affected individuals.

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Overgrowth Syndromes

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Abstract: *9yr old boy presenting with features of overgrowth of body parts mainly extremities with cutaneous naevi and lipomatous deposition over back since childhood. Examination revealed wide large extremities with large fingers, scoliosis, epidermal naevi.*

Keywords: *Asymmetric overgrowth of extremities, Wide sandal gaps, Cutaneous naevi, Lipomatous deposition, CLOVES syndrome.*

Case history

A 9 year old boy presented in our OPD with disproportionate and asymmetric growth of body parts, hands, feet and fingers since birth and non itchy hyperpigmented lesions over fore arms since last 1year. No history of photophobia, visual, hearing problems. No history of respiratory distress, pain abdomen. Family history and birth history were normal with normal intelligence.

Examination

On general survey, height 135 cm, weight 45 kg, asymmetric overgrowth of extremities, abnormally large wide hands, feet, fingers and toes. Limb length discrepency (Fig 1). Skin examination revealed cutaneous nevi over upper limb (Fig 2). On examination of back, there was deposition of fatty tissue over scapular region (Fig 3). Characteristics finding of feet is presence of wide sandal gap biletrally. Examination of spine revealed presence of scoliosis.

(a) Large wide hands or feet

(b) Large fingers or toes

(c) Wide sandal gap (Fig 4)

Diagnosis:

All the features clue to a clinical diagnosis of Cloves syndrome

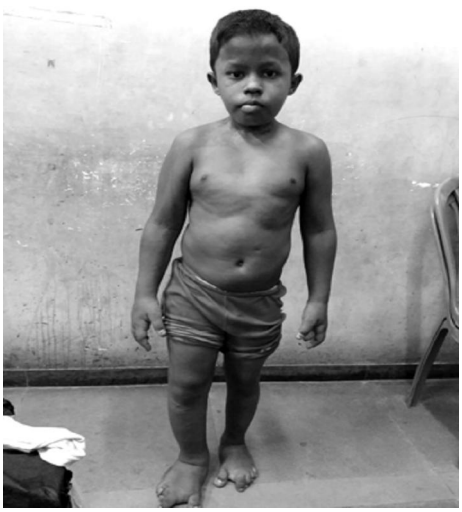

Fig 1. Limb length discrepancy

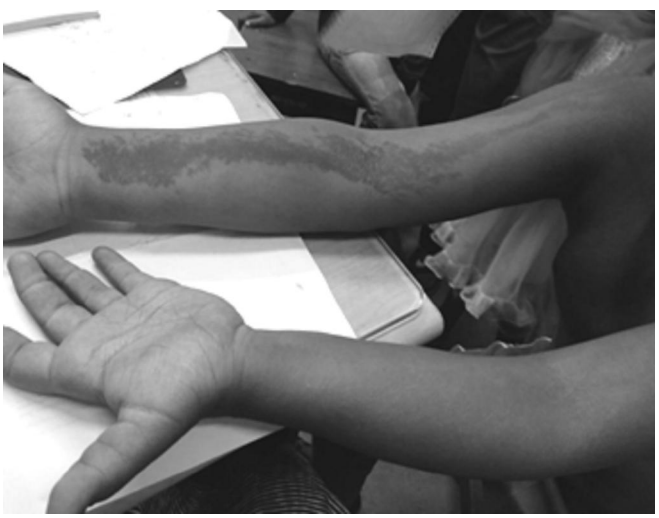

Fig 2. Epidermal nevi

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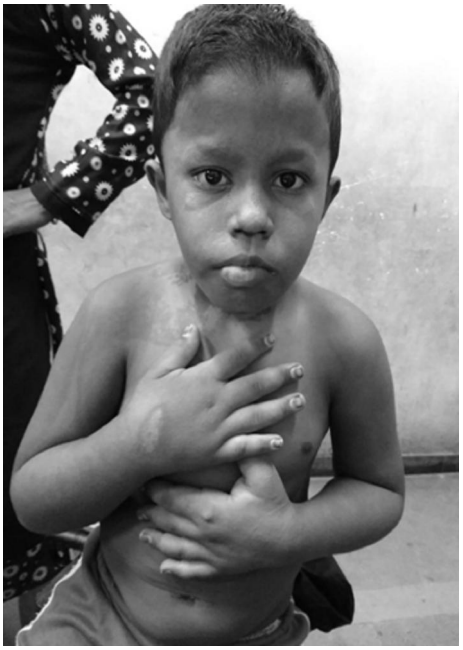

Fig 2. Cutaneous nevi

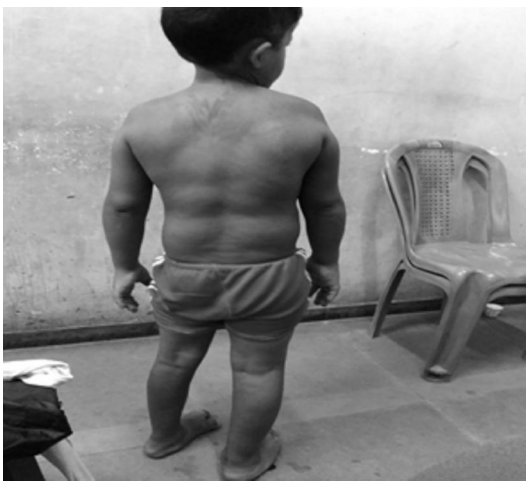

Fig 3. Lipomatous overgrowth

Fig 4. Wide sandal gap

C: Congenital – As present since birth

L: Lipomatous – Benign soft fatty tissue tumor presents since birth usually visible over back

O: Overgrowth – Abnormal increase in size in body parts . asymmetric overgrowth of extremities arms and legs with large wide fingers toes , wide gap between fingers of toes

V: Vascular malformations

E: Epidermal naevi

S: Spine / skeletal; anomalies like scoliosis

Investigations

Routine investigations like Complete Blood Count, spinal MRI to evaluate spinal dysraphism, right upper quadrant USG for Wilms tumor, echocardiography to rule out heart disease, DOPPLER study for AV malformations were done and all investigations did not support any complications.

Discussion

9 yr old boy presenting with asymmetric overgrowth of body parts mainly extremities since birth. Wide large hand foot with large fingers and toes . Characteristics wide sandal gap in foot. Boy also had fatty tissue deposition over back and nevus like lesions over upper limb, spine showed mild scoliosis. Relevant investigations done to rule out spinal dysraphism and renal tumorand vascular malformations. Diagnosis was mainly clinical. Treatment was surgery Laser, sclerotherapy, embolization and debulking operation. CLOVES syndrome (CS) is rare and evident at birth. It affects males and females equally regardless of their race or ethnicity. Many of the patients with CS are misdiagnosed as having other syndromes such as Klippel-Trenaunay syndrome (KTS) or Proteus syndrome(PS).

Related disorders

PIK3CA-related overgrowth syndromes (PROS) refers to a group of disorders caused by PIK3CA gene mutations such as CS and KTS. Only somatic mutation, no germ line mutation.

Features of the KTS and PS can be similar to those of CLOVES syndrome:

KTS is a rare disorder that is present at birth (congenital) and is characterized by a triad of

cutaneous capillary malformation (port-wine stain), lymphatic anomalies, and abnormal veins in association with variable overgrowth of soft tissue and bone. KTS occurs typically in the lower limb and equally affects both males and females.

PS is a rare disorder characterized by disorganized overgrowth of various tissues of the body. The cause of the disorder is a mosaic mutation in a gene called AKT1. Disproportionate, asymmetric overgrowth occurs in a mosaic pattern (i.e., a random "patchy" pattern of affected and unaffected areas). Affected individuals may experience a wide variety of complications that may include progressive skeletal malformations, benign and malignant tumors, malformations of blood vessels (vascular malformations), bullous pulmonary disease, and certain skin lesions. In some patients, life-threatening conditions relating to abnormal blood clotting may develop including deep vein thrombosis and pulmonary embolism.

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Rare Skin Disorder – Xeroderma Pigmentosa

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Abstract: *4 year old boy presented with progressively increasing dark brown dyspigmentary lesions mainly over sun exposed areas with extreme photophobia. IQ was normal with normal developmental milestones. No visual defect. Birth history and family history were normal.Skin biopsy for DNA repair study shows positive result for Nuclear Excision repair defect. Case was diagnosed as Xeroderma Pigmentosa. Supportive treatment was given with oral isotretinion to prevent skin cancer*

Keywords: *Dyspigmentarylesions, Freckels, Photphobia, DNA nuclear excision repair defect , Isotretinion, Skin cancer*

Case history

A 4 year old boy presented to our pediatric OPD with progressively increasing brownish black mottled dyspigmentary lesions all over body predominantly over sun exposed parts since last 2 years. The boy also had extreme photophobia. Skin lesions are rapidly progressive in nature but those were non itchy. Boy had not developed any visual problems except photophobia. No history of significant weight loss, hair changes, hearing problems or history suggestive of mental retardation. There was no other history of abdominal pain abnormal bleeding manifestations, bone tenderness or features suggestive of neurological problems. Birth history, developmental history and family history were normal.

Examination

On examination general survey was normal except presence of browinshblack mottled dyspigmentary lesions (Fig 1) all over body predominantly over sun exposed body parts. Characteristic freckles were seen over skin (Fig 2) hair changes not significant (i.e.no brittle hair except some folliculitis). Height 93 cm (within normal limit), Head circumference 48cm (normal). IQ normal , Ophthalmoscopy examination revealed no obvious abnormality.

Respiratory, cardiovascular, gastrointestinal, musculoskeletal, lymphoreticular system examination were also normal.

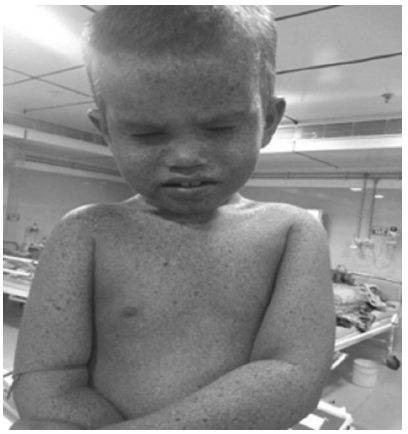

Fig 1. Mottled dyspigmentary lesions

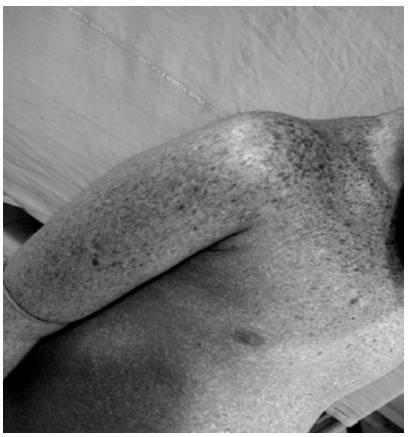

Fig 1. Freckles were seen over skin

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Investigations

Skin biopsy was taken and sent for DNA repair factor study which came positive for defect of Nuclear Excision Repair (NER) mechanism. Blood reports – complete hemogram, electrolytes, USG whole abdomen, ophthalmoscopy, chest xray found to be normal.

Management

No specific management except supportive management via protection from UV rays by wearing sunglasses, by using sunscreen cream. Oral Isotretinoin can be used for prevention of skin cancer.

Discussion

Xeroderma pigmentosa is rare skin disorder that have autosomal recessive inheritance with incidence of 1 in 100,000 worlwide, 1 in 250,000 in US and Europe and 6 times more common in Japan. Usual presenting age group is 1-2 years. Defect lies in DNA Nuclear Excision repair mechanism. Eight genes (XP A-G & V) have been discovered till now. Diagnosed by skin biopsy showing positive for DNA repair study.

Differential diagnosis are Cockayne syndrome and Trichothiodystrophy. Prognosis of this disease is very poor, most of them develop skin cancer earlier. Less than 40% live beyond 20 years age, longest survival age is 40yrs. Management is mainly supportive via protection from UV rays.Radiations are contraindicated. Oral isotretinion can be used for prevention of skin cancer.

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Infantile Alexander Disease: A Case Report

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Abstract : *Alexander disease is caused by the dominant mutations in the glial fibrillary acidic protein (GFAP) gene, on chromosome 17q21. It is named after the physician who first described the condition in 1949 (WS Alexander). Eight days old baby presented with complaints of respiratory distress with unusual large size of head. MRI brain at 1 month 4 days of age revealed diffuse hyperintesities in subcortical white matter in T2WI with frontal predominance with thin extra axial CSF intensity cystic lesions noted over both temporal lobes. Baby was diagnosed as Infantile Alexander disease after ruling out other differential diagnoses. The head circumference of the baby was kept progressing and it was 42.5cm at 1 month 4 days of age.*

Key Words: *Alexander disease, Magnetic Resonance Imaging, Head circumference, Macrocephaly, Neurodegenaration, Rosenthal fibres.*

Introduction

Alexander disease is a rare sporadic disorder which falls in the group of disorders called leukodystrophies. It is caused by the dominant mutations in the glial fibrillary acidic protein (GFAP) gene, on chromosome 17q21[1]. Alexander disease is named after the physician who first described the condition in 1949 (WS Alexander)[2,3]. Three clinical sub types have been described. The classic infantile form presents between birth and 2 years of age and is characterized by developmental retardation, progressive macrocephaly, spasticity, psychomotor retardation and unresponsive seizures causing death by 5 years; a preponderance of those affected are males. Recurrent aspiration is usual, hypotonia replaced by hypertonia, ophisthotonus posturing and scissoring is seen. The late infantile form, presenting from 2 to 7 years and the juvenile form occurs between 7 and 14 years of age and is characterized by progressive paresis with bulbar signs and hyperreflexia, and intact mental status. Adult cases are divided into two groups, depending on the presence or absence of neurologic dysfunction, the former resembling multiple sclerosis. However, the milder forms presenting later in life may not have megalencephaly[2-4]. Most of the reported cases were of infantile type with early onset macrocephaly and early death; neonatal form has been distinguished with more fatal outcome.

Metabolic abnormalities are not reported with the disease. The hallmark is the pathologic examination of the brain autopsy which shows deposition of eosinophilic hyaline bodies called Rosenthal fibers in astrocyte processes, in a perivascular distribution throughout the brain[5,6]. There are obvious disadvantages associated with a diagnosis limited to histologic confirmation secondary to a very invasive procedure – the brain biopsy. Hence the diagnosis is suggested by MRI and MR spectroscopy. MRI reveals extensive white matter changes with frontal predominance, a periventricular rim of altered signal intensity. In late stages, cysts may develop. Also involvement of caudate nucleus is specific finding for Alexander disease[6].

Case report

A 8 days old baby boy presented to our institution with jaundice from day 4 of life, respiratory distress since 4 days and apparently large head. He was born to a primigravida mother by LSCS. Indication for caesarean section was cephalopelvic disproportion. Birth weight was 4.4 kgs. Immediate postnatal period was unremarkable. Breast feeding

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initiated soon after birth. Baby was doing well till day 4 of life when he started having respiratory distress. There is no history of maternal hypothyroidism or gestational diabetes mellitus.

Physical examination revealed an alert, conscious newborn with normal growth parameters except the head circumference which was measuring 39cms (above the 97th percentile according to WHO charts). No prominent veins over forehead and no sunsetting sign was found. Anterior fontanel was wide 3.5cm x 3.5cm, fontanel tension was obviously not raised. Posterior fontanel was open and sutures were widely separated. Respiratory distress was mild with a respiratory rate of 52/min and mild chest retraction. No skin lesions or hepatosplenomegaly was found. Baby was hypotonic at presentation. There were postaxial extra digits in both upper limbs and right lower limb, no other dysmorphic features were seen. No pallor, cyanosis or edema is seen.

Workup for jaundice showed total bilirubin of 16 mg/dl, Coombs negative, no ABO incompatibility and G6PD activity within normal limits. Jaundice was treated with phototherapy.

Initial workup for respiratory distress showed chest x-ray with mild bilateral hyperinflation treated conservatively. But in due course of hospital stay the respiratory distress worsened and repeat x-ray showed a left lower lobe collapse which was treated with I.V. antibiotics and supportive care.

Later, the baby developed ophisthotonus posturing. No convulsions were witnessed. CSF examination ruled out meningitis with cell count of 3cells/cumm, protein- 93mg/dl. Cranial ultrasonography was unremarkable. CT scan of brain showed non-enhancing hypodensity within the white matter of both cerebral hemispheres which raised the suspicion of white matter disease and MRI Brain was done at 1 month 4 days of age.

Meanwhile the head circumference kept progressing and it was 42.5cm at 1month 4 days of age. MRI brain revealed diffuse hypointensities in T1WI and hyperintensities in T2WI with frontal predominance, cortical sulci are effeced, thin extra axial CSF intensity cystic lesions noted over both temporal lobes suggestive of Infantile Alexander disease.

Clinically progressive macrocephaly without accumulation of fluid is diagnostic of megaencephaly which is one of the feature of neurodegeneration. The differential diagnosis of neurodegeneration with macrocephaly are : Tay sachs, Canavan disease, Alexander disease, Metachromatic leucodystrophy, Gaucher's disease. Absence of hepatosplenomegaly excluded Gaucher's and Metachromatic leucodystrophy. Canavan's disease excluded by careful interpretation of MRI findings. Tay sach's, being a grey matter disease is ruled out by MRI depiction of white matter lesion.

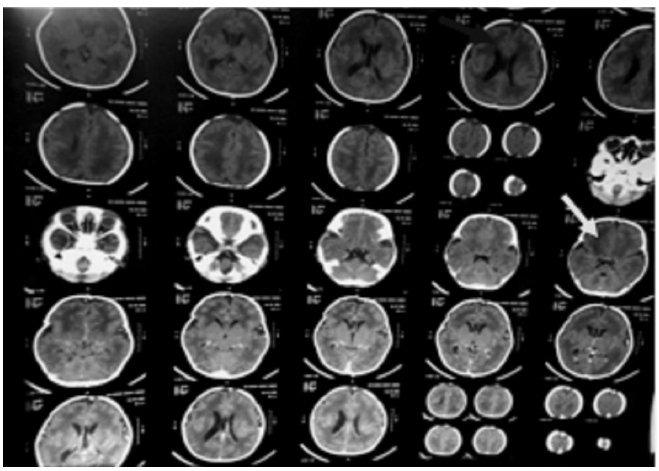

Fig 1: CT scan of brain showing hypodense subcortical white matter(red arrow) which was non enhancing after giving contrast (arrow).

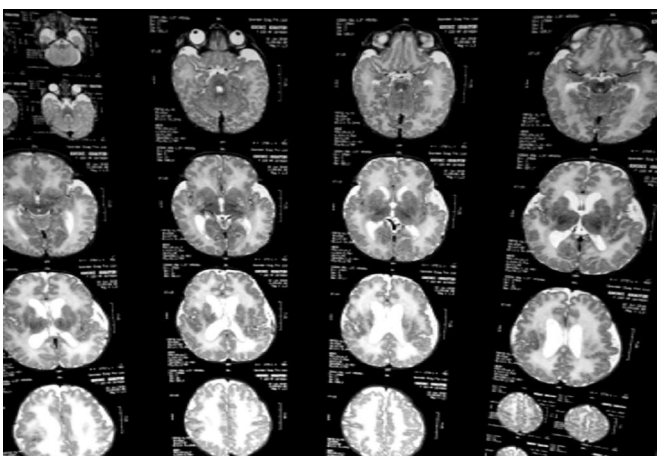

Fig 2: MRI images showing diffuse hyperintensity in T2WI involving both cerebral white matter with frontal predominance.

Discussion

Alexander disease was named after the W. Stewart Alexander, who first reported a 15 month old child with megalencephaly and psychomotor retardation

in 1949[7]. Pathological hallmark of disease is the finding of rosenthal fibers in brain autopsy. Alexander disease accounted for 1.6% of all leukodystrophies in Germany. Rosenthal fibers are not found in the astrocytes of healthy people. The major cause of the disease was defects in GFAP gene[8]. As described in the literature about the clinical sub types of Alexander disease, present case is diagnosed as an infantile Alexander disease. Generally, onset of infantile Alexander disease occurs within two years of life and often found with seizures, developmental delays, spastic paresis, psychomotor deficiencies, and macrocephaly[9,10].

Bassuk *et al*.[11] (2003), reported an infant with Alexander disease who presented with poor feeding on the first day of life, followed by emesis and weight loss. At the age of 21st day of life MRI showed signal abnormalities in the frontal lobes and basal ganglia. Over course of 25 days, head growth increased from the 50th to the 75th percentile. The child died on day 38 from prolonged seizures and respiratory failure. Heterozygous mutation in the GFAP gene detected in mutation analysis. In the present case, head circumference was progressive and it was 42.5cm at 1 month 4 days of age. MRI brain was also done at the age of 1month 4 days, it revealed diffuse hypointesities in T1W1 and hyperintesities in T2WI with frontal predominance with other signs suggestive of infantile Alexander disease. Van der Knaap *et al*.[6](2005) reported 9 patients with Alexander disease confirmed by genetic analysis who had atypical MRI features. Out of 9 cases, MRI in 8 patients showed predominantly posterior fossa lesions, especially multiple tumor-like brainstem lesions. One patient had asymmetric frontal white matter abnormalities and basal ganglia abnormalities.

Patients with genetically confirmed Alexander disease, who had no or inconspicuous cerebral white matter abnormalities and no or minimal contrast enhancement on brain MRI were also reported by Van der Knaap *et al*.[12] (2006).

Rodriguez D *et al*.[13] (2001), Goyal M *et al.*[14] (2014) also reported infantile Alexander disease presenting with macrocephaly as one of the important clinical feature. Infantile Alexander with normal head circumference is also reported by same authors. Shihara *et al*.[15] (2011) reported unusual Alexander disease without cyst formation in early MRI and long survival. In addition to the abnormalities in the frontal lobes, brainstem lesion and brain atrophy became most salient features in the progression of the disease.

In the current case report, confirmation of the diagnosis was not done by molecular diagnosis as molecular genetic laboratories are not readily available in most of the healthcare facilities in our country. However, MRI is very valuable and reliable tool in the diagnosis of white matter degeneration. But the availability of molecular genetic testing practically eliminates the need for immuno-histochemical staining of brain biopsy material as a diagnostic tool in young patients.

As stated in the literature, there is no cure for Alexander disease, and there is no stan¬dard course of treatment, it is symptomatic and supportive. The prognosis is generally poor; most children with the infantile form do not survive past the age of 6. Juvenile and adult onset forms of the disorder have a slower, lengthier course.

Though the prognosis of infantile Alexander disease is uniformly poor, accurate diagnosis is essential for prognostication and genetic counselling in order to prevent the birth of such babies in subsequent pregnancies.

Conflict of interest: None to declare

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Asphyxiating Thoracic Dystrophy without Polydactyly

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Abstract:

Asphyxiating thoracic dystrophy (ATD) is a very rare form of skeletal dysplasia that primarily affects development of the bone structure of the thorax resulting in a very narrow and bell-shaped chest[1]. Other major characteristics include kidney problems (due to renal cyst development), shortened bones of the arms and legs, extra fingers and toes, and shortstature[2]. Abnormal thorax with small ribs leads to recurrent pneumonia and varying severity of respiratory distress. We report a similar case without polydactyle[3].

Introducton

"Bell-shaped" chest a special type of thoracic dystrophy where abnormal chest cavity restricts the growth of the lungs and results in a variable degree of lung hypoplasia and breathing problem. For chest expansion we need bucket handle and pump handle movement of ribs, if ribs falls short of sternum due to chondrodysgenesis overall movement of thorax is restricted. As a result they suffer from impaired ventilation and subclinical hypoxia. Common signs and symptoms include a small chest and short ribs which restrict the growth and expansion of the lungs, often causing life-threatening breathing difficulties.

Case

Four months old male baby as in Fig 1, presented with mild cold, cough and respiratory distress for last 24 hours. There was no fever but significant feeding difficulty and sleep disturbance. History of similar illness at 2 months of age which required hospital admission. On examination baby is mildly cyanotic with oxygen saturation 88-92% in room air, respiratory rate of 56/min regular. Careful regional survey showed excess and thick skin fold in both axilla and upper thorax suggesting upward conical shape of thoracic cage simulating a "bell of a church". Excessive soft tissue and skinfold is also noted in both upper and lower limbs signifying short long bones.

Chest X ray PA view (Fig 2) showed short and horizontally oriented ribs with irregular costochondral junctions with bulbous and irregular anterior ends falling much shorter than sternum. Clavicle is placed higher up and is described as "handlebar clavicle"[4].

X ray hip (Fig 3) showed dysplastic short and square ilial bones. Tubular bones (Fig 4) are short with

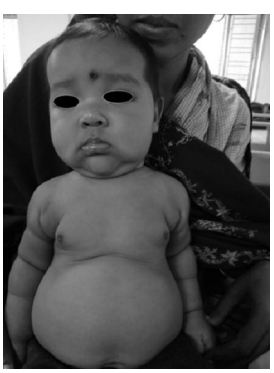

Fig 1. Thoracic dystrophy

Fig 2. Chest X ray

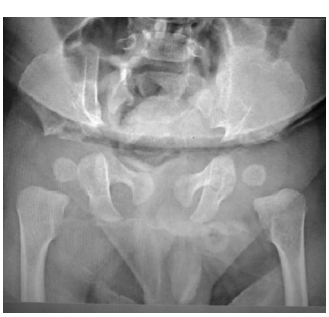

Fig 3. X ray Hip

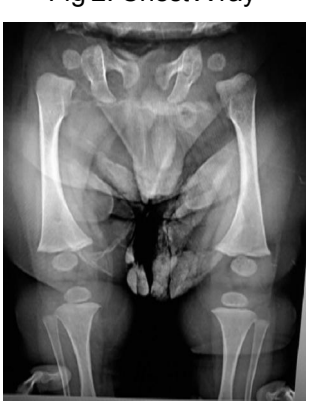

Fig 4. X ray Long bones

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bulbus ends[4].

Abnormal ribcage restrict the lung for full expansion and sufficient intrathoracic negative pressure is not generated leading to persistant low grade hypoxia. This accounts for poor mucocillary clearance, recurrent pneumonia and respiratory distress. In our case pulmonary infection took two weeks to respond with antibiotcs and nebulization. No other abnormality is found in kidney, liver, pancreas and eye.

Discussion

Thoracic chondrodystrophy and conical thorax arising out of abnormal chondrocytes was first described by Jeune et alin the year 1955, in a pair of siblings with severely narrowed chests. Children with Jeune Syndrome often present in the neonatal period with respiratory distress and recurrent infections. Lung hypoplasia, due to a restricted thoracic cage, is the major cause of death in infancy. Some people with asphyxiating thoracic dystrophy are born with less severe skeletal abnormalities, may not present in neonatal period as in our case, but as they grow older signs and symptom are florid.Few can have only mild breathing difficulties and they live into adolescence or adulthood.

Jeune asphyxiating thoracic dystrophy (JATD) is an autosomal-recessive ciliopathy associated mainly with a mutation in IFT80 gene[5] located on chromosome 15 q13 and DYNC2H1 gene[6] on 11q22.3. This gene is responsible for intraflagellar transport (IFT) for building and maintaining the structure and function of primary cilia. This mutation results in shortened or abnormal cilia directed much away from articular surface leading to abnormal position of chondrocytes and rib shortening. Most of the bones in the body develop through a process called endochondral bone formation, which starts with embryonic mesenchymal cells condensing at the sites where the skeletal elements will form . The condensed mesenchymal cells then undergo differentiation to become chondrocytes and future bone. The cilia will guide the chondrocytes to the target site. Defect in the normal structure and function of the primary cilia is responsible for some other diseases like polycystic kidney disease, kartagener and heterotaxysyndrome.

Polydactyle is not an universal criteria of Jeune syndrome, rather it is an occasional finding[7]. The absence of polydactyly as in our case excluded the diagnosis of Short rib polydactyle syndrome (SRPS) and Ellis-van Creveld syndrome (EVCS) which show its presence in at least one limb.

Now a days researcher are doing thoracic reconstruction and enlargement of the thoracic cage by sternotomy and fixation with bone grafts or a methylmethacrylate prosthesis plate[7] to promote thoracic growth. Alternatively a vertical expandable prosthetic titanium rib is a safe tool for the treatment of children with thoracic insufficiency syndrome.

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Fibrodysplasia Ossificans Progressiva (FOP) – A Case Report

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A 16 years male presented to the Pediatric Orthopaedic OPD at Institute of Child Health, with complain of pain in his right knee for 2 months and inability to walk properly. This boy developed progressive stiffening of his left shoulder girdle, chest wall and gross deformity of the spine and a fixed pelvis. He had waxing and waning of symptoms and episodic exacerbations since he was about 10 years of age. There is history of recurrent chest infections and inability to fully open his mouth. The clinical photographs demonstrate the classical features of a very rare genetic disorder called Fibrodysplasia ossificans progressiva as shown in figures (1-4).

What is FOP ?

Fibrodysplasia ossificans progressiva (FOP) is a severely disabling heritable disorder of connective tissue characterized by progressive heterotopic ossification that forms large amounts of qualitatively normal bone in characteristic extraskeletal sites. Congenital malformations of the great toes is a constant characteristic feature in FOP.

Synonyms :

The synonyms are Stoneman Syndrome, Myositis Ossificans Progressiva.

This very rare genetic disorder is classified as an Orphan Disease.

It is classified as follows - ORPHA:337 or ICD-10 M61.1 or GARD 6445.

Clinical presentation and progression of disease

Children who have FOP appear normal at birth except for congenital malformations of the great toes (hallux valgus, malformed first metatarsal, and/or monophalangism). During the first decade of life, sporadic episodes of painful soft tissue swellings (flare-ups) occur which are often precipitated by soft tissue injury, intramuscular injections, viral infection, muscular stretching, falls or fatigue. If diagnosis of FOP is suspected, any invasive intervention (such as biopsy), which may lead to flare-ups, is contraindicated. These flare-ups transform skeletal muscles, tendons, ligaments, fascia, and aponeuroses into heterotopic bone, rendering movement impossible. Patients with atypical forms of FOP have been described. They either present with the classic features of FOP plus one or more atypical features (e.g. intercurrent aplastic anemia, craniopharyngioma, childhood glaucoma or growth retardation) (FOP plus), or present major variations in one or both of the two classic defining features of FOP (e.g., normal great toes or severe reduction deficits of digits) (FOP variants).

Muscle tissue and connective tissue such as tendons and ligaments are gradually replaced by ossified bone outside the skeleton (extra-skeletal or heterotopic bone) that constrains movement.

This process generally becomes noticeable in early childhood, starting with the neck and shoulders and proceeding down the body and into the limbs.

Extra-skeletal bone formation causes progressive loss of mobility as the joints become affected. Inability to fully open the mouth may cause difficulty in speaking and eating. Over time, people with this disorder may experience malnutrition due to their eating problems. They may also have breathing difficulties as a result of extra bone formation around the rib cage that restricts expansion of the lungs.

In some cases, onset of abnormal bone growth may not occur until late adolescence or early adulthood.

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Fig 1

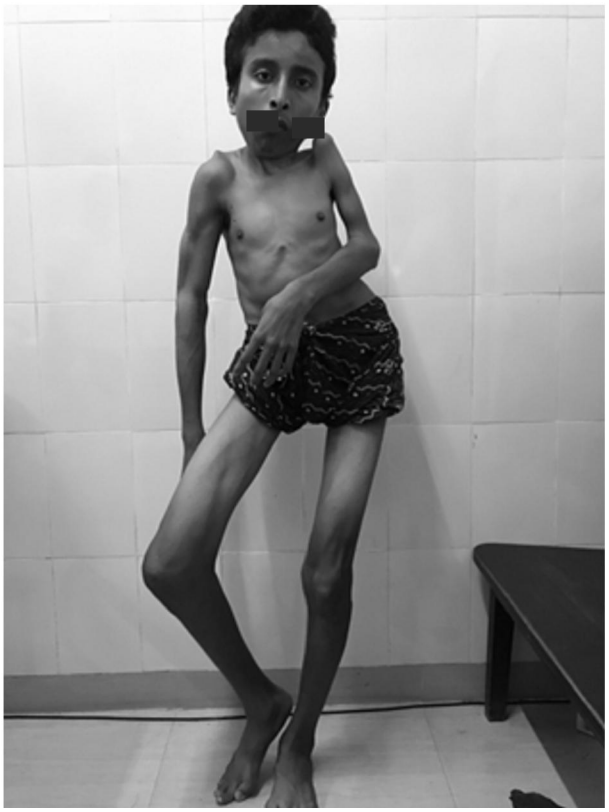

Fig 2

Fig 3

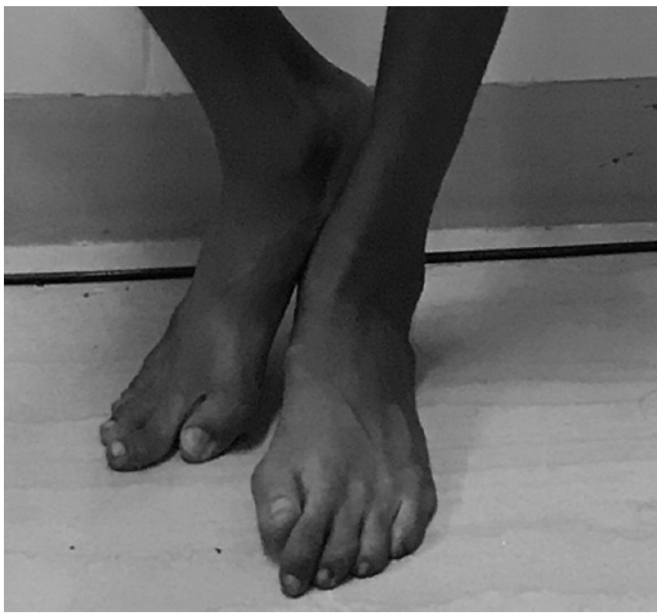

Fig 4

Fig 1 to 4 showing various deformities of Fibrodysplasia ossificans progressive (FOP)

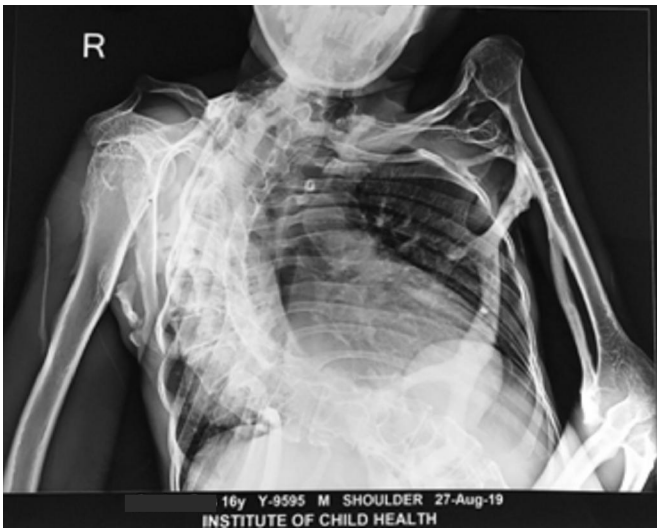

Fig 5

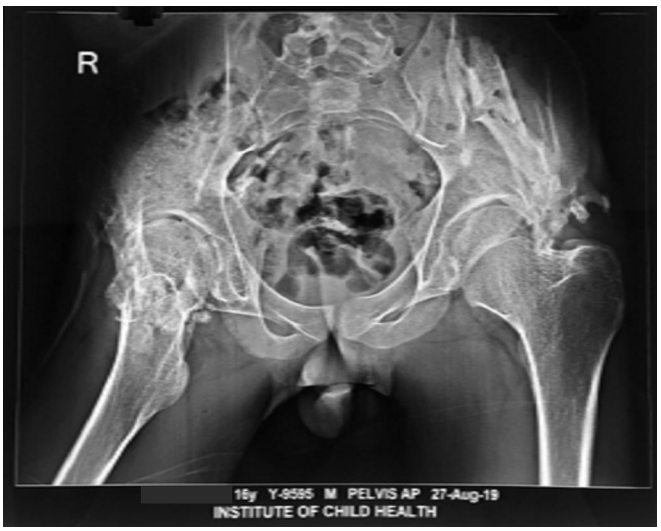

Fig 6

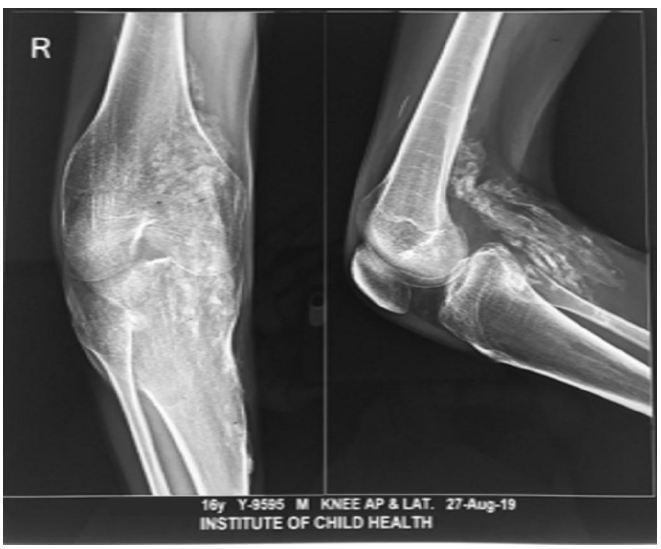

Fig 7

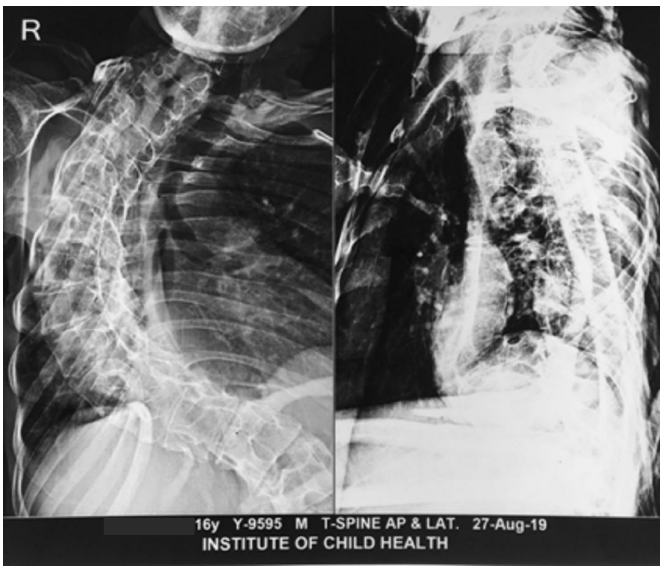

Fig 8

Fig 5 to 8 showing various raiologhical features of Fibrodysplasia ossificans progressive (FOP)

Affected individuals may have periods of time where they are free of new episodes of bone growths. However, new bone growth may begin at any time for no apparent reason (spontaneously).

Incidence or frequency of occurrence

The worldwide prevalence is approximately 1 in 2 million people. There is no ethnic, racial, gender, or geographic predilection to FOP It was first identified in the 17th century. Of an estimated 3000 affected individuals worldwide, there are approximately 800 known patients.

Diagnostic methods

The diagnosis of FOP is made by clinical evaluation. Plain radiographs showing presence of heterotopic ossification and characteristic great toe abnormality may clinch the diagnosis (Fig 5 to 8). Confirmatory genetic testing is available. Biopsy is contraindicated.

Differential diagnosis

Differential diagnosis includes progressive osseous heteroplasia, osteosarcoma, lymphedema, soft tissue sarcoma, desmoid tumors, aggressive juvenile fibromatosis, and non-hereditary (acquired) heterotopic ossification.

Antenatal diagnosis

Prenatal testing is not yet routinely available.

Management and treatment

There is currently no definitive treatment. However, a brief course of high-dose corticosteroids, such as Prednisone, started within the first 24 hours of a flare-up, may help reduce the intense inflammation and tissue swelling seen in the early stages. Other medications, such as muscle relaxants, mast cell inhibitors, and aminobisphosphonates, if appropriate, should be closely monitored by a physician. Surgery to remove heterotopic and extra-skeletal bone is risky and can potentially cause painful new bone growth. Preventive measures for physical trauma, viral infections, flu and respiratory care, spirometry may help.

ORPHAN drug

An orphan drug is a pharmaceutical agent developed to treat medical conditions (orphan diseases) which, because they are so rare, would not be profitable to produce without government assistance.

The assignment of orphan status to a disease and to drugs developed to treat it is a matter of public policy and has yielded medical breakthroughs that might not otherwise have been achieved, due to the economics of drug research and development.

3 Orphan drugs are under evaluation in clinical trials for treatment of FOP :

(i) 4-6-4-(piperazin-1-yl)phenyl-pyrazolo (1,5-a]pyrimidin-3-yl) quinoline hydrochloride

(ii) Human monoclonal antibody against activin A

(iii) Palovarotene

Prognosis

The median lifespan is approximately 40 years of age. Most patients are wheelchair-bound by the end of the second decade of life and commonly die of complications of thoracic insufficiency syndrome.

Genetic basis and inheritance pattern of FOP

Most cases of FOP occur sporadically. Where a familial pattern has been identified, FOP is inherited as an autosomal dominant trait with complete penetrance.

Bone morphogenetic proteins are regulatory proteins involved in the embryonic formation and after-birth (post-natal) repair of the skeleton. The gene identified as the FOP gene encodes a BMP receptor called Activin Receptor Type IA, or ACVR1, one of four known BMP Type I receptors. BMP receptors help determine the fate of the stem cells in which they are expressed. Classic FOP occurs when a particular amino acid in the ACVR1 protein is substituted for another amino acid at a specific location.

Chromosomes, present in the nucleus of human cells, carry the genetic information for each individual. Human body cells normally have 46 chromosomes. Pairs of human chromosomes are numbered from 1 through 22, and the sex chromosomes are designated X and Y. Males have one X and one Y chromosome, and females have two X chromosomes. Each chromosome has a short arm designated “p” and a long arm designated “q”. Chromosomes are further subdivided into many numbered bands, which specify the location of the thousands of genes that are present on each chromosome. For example, chromosome 2q23-24 refers to a location between bands 23 and 24 on the long arm of chromosome 2.

Genes are on the chromosomes that are inherited from the father and the mother. Phenotypic variation (including genetic diseases) is determined by the genes that specify a particular trait.

Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary for the appearance of the disease. The abnormal gene can be inherited from either parent, or can be the result of a new mutation (gene change) in the affected individual. The risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy, regardless of the sex of the resulting child.

FOP is caused by a mutation of a gene on chromosome 2 (2q23-24) for a receptor in the BMP signaling pathway called ACVR1.

The ACVR1 gene provides instructions for producing a member of a protein family called bone morphogenetic protein (BMP) type I receptors. The ACVR1 protein is found in many tissues of the body including skeletal muscle and cartilage. It helps to control the growth and development of the bones and muscles, including the gradual replacement of cartilage by bone (ossification) that occurs in normal

skeletal maturation from birth to young adulthood.

Researchers believe that a mutation in the ACVR1 gene may change the shape of the receptor under certain conditions and disrupt mechanisms that control the receptor's activity. As a result, the receptor may be constantly turned on (constitutive activation). Constitutive activation of the receptor causes overgrowth of bone and cartilage and fusion of joints, resulting in the signs and symptoms of FOP.

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

Most cases of FOP result from new mutations in the gene. These cases occur in people with no history of the disorder in their family. In a small number of cases, an affected person has inherited the mutation from one affected parent.

Misdiagnosis of FOP is common but can be avoided simply by examining the individual's toes for the characteristic feature, short great toes. The diagnosis may be confirmed by a thorough clinical evaluation, characteristic physical findings, and sequencing of the ACVR1 gene.

Genetic counseling

Although most cases of FOP are sporadic (non-inherited mutations), a small number of inherited FOP cases show germline transmission with an autosomal dominant pattern.

Why do we need to study such a rare disease?

Study of this very rare disease, a nature's aberration, may throw light on the missing links in bone morphogenesis and bone biology. The irreversible and till now untreatable sorrow of a few patients might one day give answers to heal millions of people affected with bone diseases.

Online resources

1) https://rarediseases.info.nih.gov/diseases/6445/fibrodysplasia-ossificans-progressiva
2) https://www.orpha.net
3) https://rarediseases.org
4) https://ghr.nlm.nih.gov
5) https://www.ncbi.nlm.nih.gov/gtr/all/tests
6) https://www.rarediseasereview.org
7) https://fopindia.org
8) http://www.musculardystrophyuk.org
9) https://www.ifopa.org
10) https://ordindia.org (Organisation for Rare Diseases India)