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Editor:

Dr. Bhaskar Shenoy

Head, Department of Paediatrics,
Chief, Paediatric Infectious Diseases Division,
Manipal Hospital, 98, HAL Airport Road,
Bangalore – 560 017, India.
Email: editor2019kpj@gmail.com

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Karnataka Paediatric Journal

Editorial

Editorial

Bhaskar Shenoy

Department of Pediatrics, Division of Pediatric Infectious Diseases, Manipal Hospital, Bengaluru, Karnataka, India.

***Corresponding author:**
Bhaskar Shenoy,
Department of Pediatrics,
Division of Pediatric Infectious Diseases, Manipal Hospital,
Bengaluru, Karnataka, India.

editor2019kpj@gmail.com

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Tuberculosis (TB) is one of the world's deadliest infectious killers. As per the WHO, every day, over 4100 people lose their lives to TB and about 28,000 people fall ill with this disease. Deaths from TB have risen in 2020 for the 1st time in more than a decade. According to the WHO, in 2020, around 9,900,000 people fell ill with TB and died, around 1,500,000. Since 2000 year, 66,000,000 lives have been saved by efforts taken globally to end TB. However, the COVID-19 pandemic has reversed years of progress made in the fight to end TB. For the 1st time in over a decade, TB deaths increased in 2020. Despite significant progress over the past decades, TB continues to be the ninth leading cause of death worldwide.

Faced with these challenges, centers for disease control (CDC) and its partners have proven resilient and adapted services to sustain TB screening and treatment activities. CDC leads a state-of-the-art national TB program and conducts clinical trials and epidemiologic research that contributes to new diagnostics, treatments, and approaches for eliminating TB. This year, CDC published guidance for a new treatment regimen for extensively drug-resistant TB disease and a shorter 4-month regimen to treat drug-susceptible TB disease.

World TB Day is observed on 24 March to spread awareness about the disastrous health, social and economic consequences of TB and to take efforts to end the TB epidemic globally. World TB Day is celebrated to educate people around the world about the disease TB and its impact. The date marks the day in 1882 when Dr. Robert Koch announced that he had discovered the bacterium that causes TB, which opened the way toward diagnosing and curing this disease.

The theme of World TB Day 2022 – "Invest to End TB. Save Lives." – conveys the urgent need to invest resources to ramp up the fight against TB and achieve the commitments to end TB made by global leaders. This is especially critical in the context of the COVID-19 pandemic that has put End TB progress at risk and to ensure equitable access to prevention and care in line with the WHO's drive toward achieving Universal Health Coverage. More investment will save millions more lives, accelerating the end of the TB epidemic.

The theme of World TB Day 2021 was "The Clock is Ticking." It focuses that the world is running out of time to act on the commitments to end TB made by the global leaders. The theme of World TB Day 2020 was "It's TIME." It is time to test and treat latent TB infections. It is time to educate and strengthen people regarding TB and spread awareness among healthcare providers. As it is said, for latent TB infection treatment is necessary to control and eliminate it. Furthermore, it is time to speak up. CDC's TB Personal Stories series tell the experiences of people diagnosed with latent TB infection and TB disease. CDC and several other organisations are working toward it. Further, the theme focuses that it's time to end the stigma that is the stigma associated with TB disease may also place certain populations at higher risk. Stigma may make people take medical

care or follow-up care for TB. TB can get anyone and TB people are found in every state, workplace, etc.

On this day in 1882, Dr. Robert Koch announced the discovery of a *Mycobacterium tuberculosis* that causes TB and his discovery opened the way toward diagnosing and curing this disease. We can not ignore that TB remains the world's deadliest infectious killer. Heads of State for the 1st time in 2018 came together to accelerate the response to TB in countries to reach targets and made commitments to end TB in the UN High-Level Meeting in September 2018.

National Tuberculosis Elimination Programme – previously called RNTCP is a programme for the prevention and control of TB in-country by the Ministry of Health and Family Welfare, Government of India. It has integrated four strategic pillars of "Detect – Treat – Prevent – Build" under the National Strategic Plan 2017–2025 for moving toward TB elimination by 2025. "Call to eliminate TB, by 2025 – 5 years in advance of the goals unanimously adopted by the UN General Assembly as part of the Sustainable Development Goals."

Global efforts continue to focus on strengthening national TB strategies in priority countries with high rates of TB, drug-resistant TB, and TB/HIV coinfection. To sustain and expand TB activities during the COVID-19 pandemic, CDC adapted TB screening and treatment services, incorporating digital care strategies, multi-month dispensing of medicines, and services designed for individual community needs.

COVID-19 setbacks highlight the fragility of hard-won gains made recently toward global TB elimination targets. Unless TB prevention and treatment efforts are intensified, the United Nations' TB targets of treating 40 million people and providing TB preventative treatment to 30 million people will likely remain out of reach. However, we have also learned a lot over the past few years – to innovate, adapt and act boldly and decisively. By applying these lessons learned, we can make progress toward these global goals.

Timely diagnosis of TB disease saves lives and prevents the spread of TB in our communities. We must regain the momentum lost due to COVID-19 and accelerate progress in saving lives, reaching global TB targets, ensuring equitable access to TB services and achieving our goal of eliminating TB. We should work together to eliminate TB in the country and around the world.

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Karnataka Paediatric Journal

Review Article

All about scrub typhus

Sunil Kumar Agarwalla

Department of Pediatrics, SVPPGIP, Cuttack, Odisha, India.

***Corresponding author:**
Sunil Kumar Agarwalla, Department of Pediatrics, SVPPGIP, Cuttack, Odisha, India.

sunil_9910@yahoo.com

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ABSTRACT

Introduction: Rickettsia is Gram-negative, non-motile, obligate intracellular proteobacteria. They stay in various forms such as coccus, bacillus, and threads. At times, they are regarded as coccobacilli. No human-to-human transmission is there. They always need a vector such as fleas, lice, mite, and ticks for transmission. Rickettsiae species were classically divided into spotted fever and typhus groups. Scrub typhus also known as bush typhus is an important cause of acute febrile illness in South and East Asia and Pacific. It is caused by the intracellular parasite *Orientia tsutsugamushi*, a gram negative alpha proteobacterium of family Rickettsiaceae which was first isolated and identified in 1930 in Japan. It is distinct from other Rickettsiae in that it lacks both peptidoglycan and lipopolysaccharide in its cell wall. Like other vasculotropic rickettsiae, it affects vascular endothelial cells causing vasculitis. It also affects macrophages and cardiac myocytes.

Objectives: This review will give a way forward regarding all information about scrub typhus in detail.

Materials and Methods: Various clinical profile especially clinical features, presence or absence of ESCHAR, organ invovement, investigations, treatment and final outcome was studied in detail.

Results: Clinical results, investigations were analysed to stamp the diagnosis. Different modalities of management has interpreted well.

Conclusion: Among all rickettsial infections, scrub typhus being most common is seen all over Indian states and UTs. A child presenting to ER with fever of unknown origin, nephropathy, acute encephalitic syndrome, hepatosplenomegaly, lymphadenopathy, and also hypotension pointing toward possibility of scrub, hence, a detailed search for ESCHAR being essential in clinical examination.

Keywords: Rickettsia, Scrub typhus, Orientia, Vasculitis

INTRODUCTION

An estimated 1 billion people are at risk for scrub typhus and 1 million cases occur annually.[1] Scrub typhus occurs mostly in Asia including areas delimited by Korea, Pakistan, and North Australia. In India, it is reported from almost all states and union territories. The 1st case was reported from Punjab (Juyal *et al*., 1992). Infections commonly occur in rainy months mostly June–October. Once thought to be disease of rural population, these infections are being increasingly reported from urban areas of India.

TRANSMISSION

The infection is transmitted through the bite of chigger (larval mite) of a trombiculid mite (*Leptotrombidium*), which serves as both vector and reservoir. Vertical transovarial transmission

(passage of the organism from infected mites to their progeny) is the major mechanism. Because only the larval stage takes blood meals, a role for horizontal transmission from infected rodent hosts to uninfected mites has not been proved.

PATHOGENESIS

From the regional node rickettsia, they find their way to different organs through blood stream. Like malaria parasite entering RBC, these coccobacilli enter endothelial cells. The main pathologic change is focal or disseminated vasculitis caused by the destruction of endothelial cells and the perivascular infiltration of leukocytes.[2] The process may be stimulated by widespread infection of vascular endothelial cells, which corresponds to the distribution of disseminated vasculitic and perivascular inflammatory lesions. They have special affliction for small and medium vessel wall causing diffuse endothelial infection (infective vasculitis). This, in turn, causes microvascular leakage and vascular lumen obstruction causing edema, hypotension, and hypoalbuminemia. There is immune-mediated inflammation leading to non-occlusive thrombosis, tissue infarction, and hemorrhage ensuing end-organ damage most often manifested in brain and lungs.

MATERIALS AND METHODS

Varied clinical presentations indicating specific investigations will point towards final diagnosis.

CLINICAL FEATURES

IP ranges from 1 to 2 weeks. Scrub typhus can be mild or severe in children and can affect almost every organ system. Clinicians should be aware of four systemic presentations:

1. Central nervous system (CNS)
2. Respiratory
3. Renal
4. Gastric intestinal tract (GIT).

Diagnosis is mainly based on strong clinical suspicion in a background of undifferentiated fever/fever without focus for more than 5 days, high grade, abrupt onset associated with headache, myalgia, arthralgia not responding to conventional antibiotics, and a presence of eschar. Hepatosplenomegaly, regional and generalized lymphadenopathy, and edema (periorbital edema, pedal edema, and anasarca) have also been reported. It can even mimic sepsis of unclear etiology or dengue-like disease picture.

GI symptoms such as abdominal pain, nausea, vomiting, diarrhea, hepatitis, surgical abdomen, and acute gastroenteritis occur in 40% of patients. Even acute renal failure can be a presenting feature of rickettsial disease. It can cause fever with cough and pulmonary infiltrates or community acquired pneumonia and even non-cardiogenic pulmonary edema. Aseptic meningitis, meningoencephalitis, and acute encephalitic syndrome (AES) are potential fatal complications of scrub. High index of suspicion is required to diagnose scrub meningoencephalitis in a child presenting with fever, headache, and altered sensorium with or without convulsion. Neurological manifestation is either due to systemic (CNS) vasculitis or direct invasion by the organism.

ESCHAR is typical for SCRUB TYPHUS and is seen in 7–68% of cases. It is a crusty necrotic lesion with or without surrounding erythematous halo. It is usually single, painless, non-pruritic and about 1 cm in diameter resembling the skin burn of cigarette and caused by necrosis of dermal and epidermal tissues with superficial crust densely infiltrated with lymphocytes, histiocytes, damaged capillaries, and venules. One should search for eschar in the area of draining lymphadenopathy as painful regional lymphadenopathy is a marker of hidden or developing eschar. Eschar is considered as pathognomonic of rickettsial diseases, though it can be seen in anthrax, bacterial ecthyma, spider bite, and rat bite fever [Figures 1 and 2].

LABORATORY RESULTS

Laboratory investigations reveal normal to low total leukocyte count, thrombocytopenia, raised ESR and CRP, hyponatremia, hypoalbuminemia, and elevated hepatic transaminases serum glutamic pyruvic transaminase {SGPT>SGOT) serum glutamic-oxaloacetic transaminase. Cerebrospinal fluid (CSF) examination reveals mild mononuclear pleocytosis with normal glucose levels. Chest radiography reveals transient perihilar peribronchial interstitial infiltrates. Rash in scrub typhus is maculopapular, uncommon than spotted fever group seen in 30–43% of cases.

Although rickettsiae can be isolated from or detected in clinical specimens, serological tests still remain an indispensable tool in the diagnosis.[3] Diagnosis is confirmed by rickettsial DNA detected in whole blood or tissue samples, or 4-fold rise in antibody titers on acute and convalescent sera by immunofluorescence assay (IFA) or immunoperoxidase assay. IFA is the gold standard test but has disadvantages of being expensive, not easily available and requiring expertise sophisticated instruments. Orientia serological tests such as indirect fluorescent antibody are >90% sensitive with 11 days or more fever. Rickettsia can be cultivated using tissue culture methods. In India, where PCR and IFA are not easily available, properly performed paired serological like IgM ELISA has high positive predictive value.

Weil-Felix (heterophile agglutination) has lower sensitivity but better specificity, inexpensive, easily available, not

requiring expertise instruments. It gives a positive result with OXK titer of 1:80 or more in scrub typhus.

RISK FACTORS

People having animal sheds in proximity of homes or exposure to rodents, living in or travel to areas endemic for rickettsial diseases, overcrowding and poor personal hygiene, war, famines all predisposes to these infections.

DIFFERENTIAL DIAGNOSIS

D/D includes fever of unknown origin, typhoid fever, dengue hemorrhagic fever, other rickettsioses, tularemia, anthrax, dengue, leptospirosis, malaria, infectious mononucleosis, meningococcemia, adverse drug reactions, and vasculitis such as Kawasaki disease, COVID vasculitis, MISC during COVID pandemic, and thrombotic thrombocytopenic purpura.

TREATMENT

Suspected cases are treated empirically for management protocol see Figure 3. Careful hemodynamic management should be done to avoid pulmonary and cerebral edema.

The drug of choice is doxycycline (4.4 mg/kg/day divided every 12 h PO or IV (max200 mg/day). Intravenous doxycycline (monotherapy) is sufficient to treat children with meningoencephalitis (total duration 7 days). It is broad-spectrum antibiotic of tetracycline class. It inhibits bacterial protein synthesis by binding to 30s ribosomal subunit. It has bacteriostatic activity against a broad range of Gram – ve and Gram +ve bacteria. Oral/intravenous is safe during breastfeeding. Therapy should be continued for a minimum 5 days and until the patient is afebrile for at least 3 days.

Side effects are diarrhea, nausea, vomiting, increased risk of sunburn, and use during the first trimester causes permanent discoloration of teeth.

Alternative regimens include tetracycline (25–50 mg/kg/day divided every 6 h PO: Maximum 2 g/day) or chloramphenicol (50–100 mg/kg/day divided every 6 h IV max 4 g/day). It is preserved for pregnant women and for patients with doxycycline allergy.

Macrolides such as clarithromycin (15–30 mg/kg/day per oral divided every 12 h, max 1 g/day) or azithromycin (10 mg/kg PO on day 1, then 5 mg/kg PO; maximum: 500 mg/day), fluoroquinolones, and rifampicin (especially used for pregnant women) are other effective regimens. Sulfonamides are contraindicated.

As per Mathai *et al*., 17 patients treated with doxycycline recovered in 1–3 days, as well as two patients who received chloramphenicol. In five patients who received ciprofloxacin,

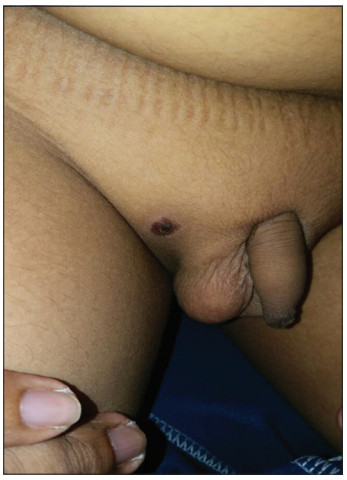

Figure 1: An eschar in R inguinal region.

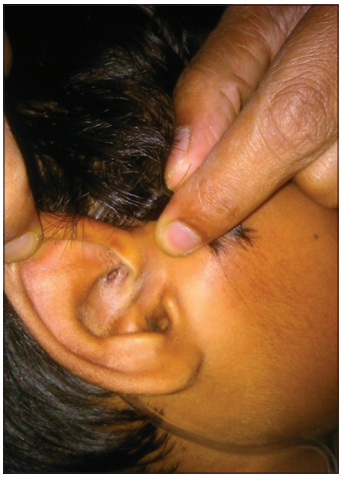

Figure 2: An eschar inside R pinna.

fever subsided only after 5 days. Finally, 3 patients (10.7%) died, including one patient treated with doxycycline.[4]

COMPLICATION

Serious complications include pneumonia in 20–35% and meningoencephalitis in approximately 10–25% of children. Acute renal failure, myocarditis, and a septic shock-like syndrome occur much less often. Gangrene, acute respiratory distress syndrome, gastrointestinal bleed, neurological sequelae, hemophagocytic lymphohistiocytosis, purpura fulminans, myocarditis, and disseminated intravascular coagulation (DIC) can also occur. The infection carries a high of mortality (death rate up to 30%) if timely interventions not done.

Few cases of complicated scrub also revealed positive anti-COVID antibody. As of now in India, COVID vaccination has not started U18, it implied either COVID being as coinfection or mere a coincidental finding suggestive

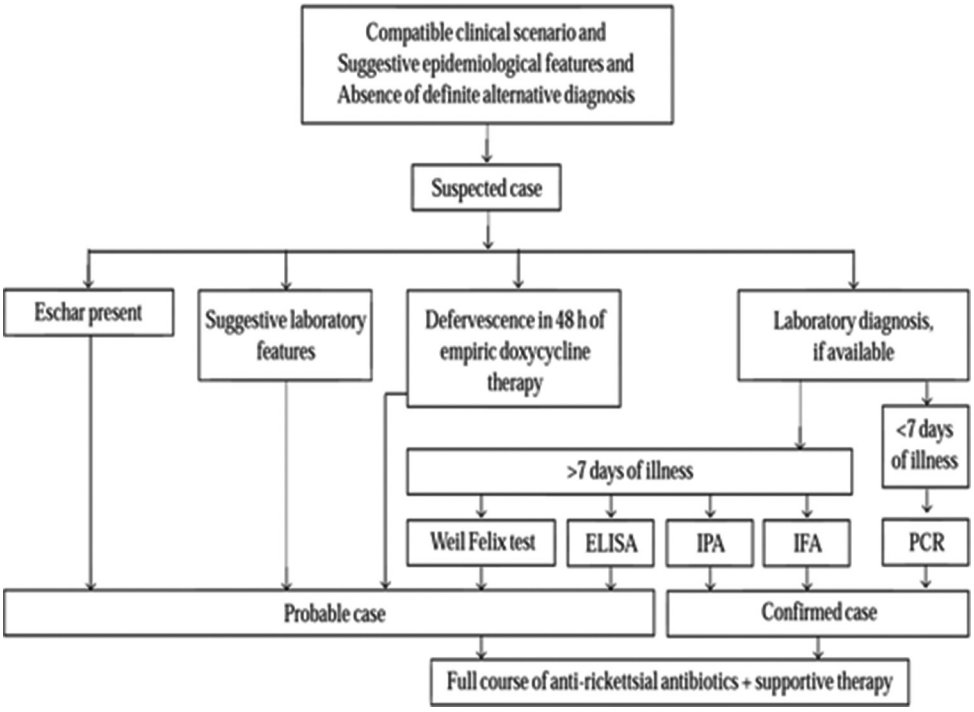

Figure 3: Management algorithm for rickettsial infections. ELISA: Enzyme-linked immunosorbent assay, IPA: Immunoperoxidase assay, IFA: Immunofluorescent assay, PCR: Polymerase chain reaction.

of past infection. Few cases admitted as multisystem inflammatory syndrome in children (MISC) and treated in line with intravenous immunoglobulin/intravenous (IVIG/IV) methylpred shown remarkable improvement after doxycycline as per coexistent scrub diagnosis. However, COVID and MISC in children being new entity more study and research needed to understand scrub versus MISC.

As per Thap *et al*., scrub typhus with septic shock patients results in organ failure: Respiratory failure and DIC was predominant followed by renal and hepatic involvement. Laboratory findings revealed that almost all of the patients had a mild leukocytosis, reduced hematocrit, and thrombocytopenia; SGOT, alkaline phosphatase (ALP), direct bilirubin, total bilirubin, blood urea nitrogen (BUN), and creatinine (CR) were elevated; hypoalbuminemia was noted.[5]

POOR PROGNOSTIC FACTORS

G6PD deficiency, alcoholic liver disease, younger age, shorter incubation period, absence of rash, diabetes mellitus, delayed institution of anti-rickettsial drugs, and early multisystemic organ dysfunction.

PREVENTION

Vector control, avoiding over-crowding, clean protective clothing, proper hygiene practices, permethrin based (on cloth) and 20–50% DEET(N-diethy-m-toluamide)-based (on skin) insect repellants to be used, prevention of vector bite, and prompt removal of mites.

CONCLUSION

Due to low index of suspicion, non-specific clinical features in early course of disease and absence of easily available sensitive and specific diagnostic tests, these infections are difficult to diagnose. Strong clinical suspicion in a background of high fever, edema, and hepatosplenomegaly not responding to conventional antibiotics must be kept in mind. ESCHAR search, especially in flexural and intertriginous areas, should be included in routine examination of every patient with continued fever. Scrub meningoencephalitis is an upcoming differential diagnosis of acute encephalitis syndrome (AES). Cure rates are very high if treatment started on time. The clinical manifestations range from subclinical disease to organ failure and soon become fatal. Deaths are attributable to late presentation, delayed diagnosis, and drug resistance. Doxycycline is the gold standard drug and should be used judiciously. No vaccine is available due to marked genetic heterogeneity of strains.

FUTURE PROSPECTS

Research and development to focus on following issues: Vaccine development and rapid diagnostic card test for antigen and antibody.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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Karnataka Paediatric Journal

Review Article

Patenting the innovation and regulatory considerations

Bindu Sharma[1]

[1]Origin IP Solutions LLP, Bengaluru, Karnataka, India.

***Corresponding author:**
Bindu Sharma,
Origin IP Solutions LLP,
Bengaluru, Karnataka, India.

bindu@origiin.com

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ABSTRACT

Bringing a medical product in the market is far more complicated compared to any other product due to its sensitivity and direct implication to human life. On one hand, legal protection in the form of patent may be needed and on the other hand the approval to manufacture and sell product should be obtained. In this article, we will discuss the role of Intellectual Property Rights in protecting innovations as well as regulatory requirements, specifically in case of medical products.

Keywords: Patent, Medical, Innovation, Regulatory, IPR

Patent is one of the most popular forms of Intellectual Property Rights, granted by the Government for inventions that are novel, industrially useful, and comprise an inventive step. A patent is granted for a product or process and helps inventors in many ways. These ways include helping inventors gain a competitive edge in the market, securing the validity of the true and first inventors of the innovation, enhance the valuation of their company and become a revenue-generating tool when commercialized. Having a patent also helps inventors to market their product better and strengthen their reputation and goodwill in the market.

The details of the invention must be documented in a prescribed format along with fee and appropriate forms, which then have to be submitted to the patent office in order to obtain a patent. The patent application is published and duly examined (or scrutinized) by the examiner. If everything in the application is in place with respect to the subject matter claimed in the patent application, the patent is granted. Protection extended in the form of a patent usually lasts for 20 years from the date of filing, provided renewal fee by the applicant is paid in time and the patent is not objected by third party (ies).

WHAT IS REQUIRED TO GET A PATENT?

Patents are granted by the Government for inventions (either products or processes) that are novel, industrially useful, and comprise an inventive step. A patent technically comprises a techno-legal document where detailed information about the invention is submitted. Therefore, it is extremely important for the inventor to document the invention in a proper manner right in the beginning. Three main parameters are given prime important when documenting the invention. These are novel elements of the invention, technical problems for which inventor has found a solution through the invention, and lastly, working of the solution or invention [Figure 1].

The invention may be considered to be novel if with respect to the novel elements of the invention, there is no existing prior art in the form of publication or patent. There are various paid and free

databases to perform a patent search and assess the novelty of the invention. Different search techniques are used to search for relevant prior arts, where the techniques used are keyword searches, assignee searches, and so on. Since novelty plays a very important role in the entire process of getting a patent, the inventor shall maintain strict confidentiality of the invention, at least until after the patent application is filed and date of filing/priority is obtained. Disclosure of the invention in conferences, articles, or any other kind of public disclosures shall be avoided until after the patent application is filed. It's worth observing here that the inventor's own disclosure before the date of filing for a patent can stop him from getting a patent.

If the invention is novel, the inventor must assess if the invention has an inventive step. Inventive step is a feature of an invention that involves a technical advancement as compared to pre-existing knowledge or having economic significance or both, and which makes the invention not obvious to a person skilled in the art.

The third and last criteria to get a patent is that the invention must have industrial application, i.e., the invention must be capable of being used or made in the relevant industry.

Apart from fulfilling the above three conditions of patentability, the invention must further not fall into the category of "inventions not patentable," described in Section 3 and 4 of the Indian Patents Act 1970. Specifically, with respect to medical inventions, Section 3 prohibits patents on any process for medicinal, surgical, curative, prophylactic, diagnostic, therapeutic, or other treatment of human beings or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products. For example, a method to treat cancer or perform a surgery is not patentable because it is a method for the treatment of human beings. Similarly, any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products is also not patentable. An application of substance to the human body purely for cosmetic purposes is not a treatment or therapy and hence may be patented provided it fulfills the criteria of patentability.

PREPARING TO FILE FOR A PATENT

Documentation of the invention in detail is very important before a patent is to be filed. After the documentation is done, patent search is performed to assess novelty of the invention. Since filing of a patent is a tedious and expensive process, it is important to properly perform a patent search and file proceed with the patent only if the invention is novel. Due to its important, professional help may be sought to perform a patent search.

After a patent search is done and the inventor is sure about filing for a patent, the patent specification is drafted. Patent search is one of the ways to assess the novelty and patentability of the invention right in the beginning to increase the chances of getting a patent. Here, the inventor has the option of either filing a provisional or complete patent application. The first application by the inventor is often filed in his own country and thereafter, the application may be filed in foreign countries if it is so desired. If the invention is not ready and inventor needs few more months to complete it, inventor may choose to file a provisional application. In such a case, the inventor can file a provisional application to claim date of filing (priority date) and obtain a patent application number. If a provisional patent application is filed, the complete application shall be filed within 12 months from the date of filing provisional application.

RIGHT OF THE PATENT HOLDER

It is interesting to note that a patent does not give the inventor any positive rights but rather, negative rights. The patent holder or the patentee can prevent third parties from making, using, selling, offering for sale or importing the patented invention, in the country where he has patent protection. For example, if the patentee has an Indian patent, he can prevent third parties from making, using, selling, offering for sale, or importing the patented invention in India. However, if he do not have a patent in the USA or China, people in these countries can use his invention without his consent.

RIGHT TIME TO FILE FOR A PATENT

After performing the patent search and carrying out initial due diligence, patent application should be filed without any delay. If the product is not ready, provisional application may be filed to secure the priority date and application number, and complete specification may be filed later once the product is ready. In the entire system of patenting, the priority date or the date of first filing is very important as patents are granted on a first-come-first-serve basis.

The invention is also required to be novel on the date of filing. Considering these factors, it is highly recommended to file a patent application at the earliest, taking help from a registered patent agent. The Indian Patent Office (IPO)[1] has a list of registered patent agents who authorized to draft and file patent applications on behalf of inventors in India as well as PCT. The list of registered patent agents may be obtained from the official website of the IPO. A patent agent is a person who is at least a graduate in science and has cleared the Indian Patent Agent examination following which, his name is registered in the register of patents as a registered patent agent. Since technology is evolving day by day, it is becoming increasingly more important to select a patent

agent who is capable enough to handle invention from a particular scientific domain.

When patenting a product, it must be checked if a design patent is also attainable for the invention. The design of an invention, also called as Industrial design refers to the aesthetic look and feel of the invention and requires formal registration of the same. Brand name of the product or trademark is a valuable intangible asset and often includes the name, logo, and tagline of the brand name. In order to ensure that the trademark does not imitate any existing marks, a trademark search should be performed before registering the trademark. Further, the trademark should not be suggestive or descriptive in nature with regards to the product it is being used for, and hence arbitrary trademarks are generally easy to register.

STEPS TO REGISTER A PATENT

As soon as a patent application is filed in India, the receipt of the filed application containing the priority date and application number is obtained. Almost all timelines are calculated from this date of first filing, also called the priority date. Publication of the application on the official website of the IPO takes place after passage of 18 months of time, starting from the priority date. However, there are provisions to expedite the publication of the application if it is required for the application to be published sooner [Figure 2].

After publication, the application is taken up for examination where the Examiner examines it and issues first statement of objections, to which the inventor must reply within 6 months from the date of issuance. After the Controller is satisfied with the application, the patent is granted. To keep the patent enforced, the inventor must pay a renewal fee periodically. If required, foreign filing is initiated within expiry of 12 months from the priority date.

FILING FOR A PATENT IN FOREIGN COUNTRY (ies)

As patent rights are territorial in nature, patent applications should be filed in every country that the inventor desires to have their invention patented. However, the first patent application must be filed in the inventors' home country to obtain the priority date. There are two ways to file a patent application in foreign countries, and are as given below:

Convention application route

This route is preferred when a patent application is be filed in only two or three foreign countries.[2] The patent application may be filed in countries that are part of the Paris Convention, and the patent application so filed is called a convention application. For example, a resident of India wants to file their application in the United States and Japan. Both of these countries are part of the Paris Convention, so the inventor may opt to go for the convention route to proceed with the foreign patent applications. The resident of India must first file their invention in India to obtain a priority date, where the application filed in India is called a Basic Application. The convention application must be filed in the countries of Japan and the United States within 12 months from the priority date. The application filed in these countries is called Convention Application and in this way, it becomes possible for the inventor to seek patent protection in convention countries. As of now, around 168 countries are members of the Paris Convention, covering all important jurisdictions. It must be noted that the Indian patent agent who filed the patent application in India is not authorized to file and prosecute patent application in foreign countries and it is up to the inventor to engage with local patent agents or attorneys in foreign countries to file their application in the respective countries.

Patent cooperation treaty (PCT) route

PCT[3] route is helpful when an inventor wants to file their application in multiple countries. PCT route is a cost-effective way to file their application in multiple countries and gives additional time to the inventor to decide about the countries where they want to file their application. Similar to convention filing, the PCT route requires the inventor to file their application first in his country and obtain a priority date. Within 12 months from the priority date, a single PCT application must be filed. PCT application can conveniently be filed online by the India patent agent. After the application is filed, it is examined by International Search Authority (ISA) and a comprehensive report on patentability is generated, which assesses novelty, non-obviousness, and industrial applicability of the invention. The comprehensive report is a good document for reference as it helps inventor to understand how strong his invention is. Within 30 or 31 months from the priority date, the inventor can file his application in any member states of PCT, and this application is called PCT-National phase application. It is to be noted that PCT is only patent filing platform and it does not grant patent. PCT only enables filing of patent application in its member states and helps inventor assess patentability of their invention. Additionally, PCT provides a time of 18 months from priority date to enter PCT national phase, as opposed to 12 months of time that the convention route provides.

PRODUCT LAUNCH AND INFRINGEMENT RISK

Having a granted patent does not necessarily guarantee that the invention is safe to be launched in the market by the

inventors. In order to launch the product, it is important to assess if any feature of the product is infringing patent rights of others or not. If performed in the beginning, appropriate due diligence can save the inventor from lot of disputes later on. It is generally called clearance search or Freedom-to-operate search, wherein patents disclosing features about each novel element of the invention are analyzed, and assessed to give opinion on patent infringement risk.

REGULATORY APPROVALS NEEDED TO BRING PRODUCT IN THE MARKET

The purpose of filing for patent is to extend legal protection and prevent third party (ies) from making, using, selling, offering for sale, and importing the patented invention. However, in the case of pharmaceutical or medical products, it is required to seek permission from the authorities to ensure that the product is safe to be used and to verify the product has undergone required tests to prove the same. Medical products need to comply with India's medical device regulations before they can be sold in India. The Central Drug Standards Control Organization (CDSCO) is India's main national regulatory body for pharmaceuticals and medical devices. Within CDSCO, The Drug Controller General of India (DCGI)[4] is the key official responsible for the approval of the manufacturing of certain drugs, vaccines, blood products, specific medical devices, new drugs, etc. The CDSCO is responsible for regulating clinical trials of drugs and the manufacture, approval, and sale of medical devices and drugs in India. It is also responsible for providing expert advice on health issues and the enforcement of the Drugs and Cosmetics Act.

The manufacturing, import, sale, and distribution of medical devices are regulated under India's Drugs and Cosmetic Act and Rules.[5] On a whole, only 40-50 medical devices require formal registration in India. However, for all other medical devices that do not require registration, the manufacturer of the medical devices is required to obtain a No Objection Certificate (NOC) from the DCGI. NOC issued by the DCGI states clearly that the said product does not require registration in India and can be imported freely into India.

At the time of filing application for registration, the right class for the product needs to be identified and specified as below:

- Class A – Low Risk (example: thermometers, tongue depressors)
- Class B – Low-moderate Risk (example: hypodermic needles, suction equipment)
- Class C – Moderate-high risk (example: lung ventilator, bone fixation)
- Class D – High Risk (example: heart valves, implantable devices).

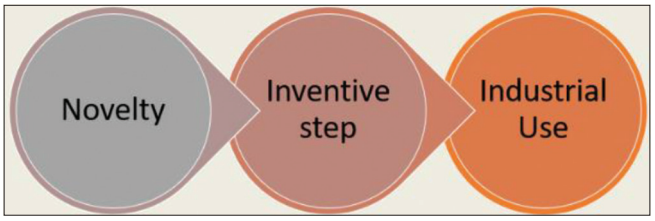

Figure 1: Criteria of patentability.

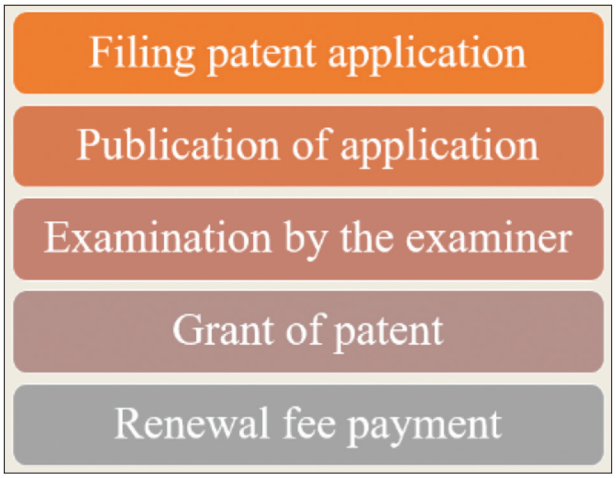

Figure 2: Main steps to register a patent.

CONCLUSION

Bringing a medical product in the market is far more complicated compared to any other product due to its sensitivity and direct implication to human life. On one hand, legal protection in the form of patent may be needed and on the other hand, the approval to manufacture and sell product should be obtained.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

To estimate the prevalence of thrombocytopaenia and its role as prognostic marker in patients of paediatric intensive care unit

Gurudutt Joshi[1], Hetal Budh[1]

[1]Department of Paediatrics, Surat Municipal Institute of Medical Education and Research, Surat, Gujarat, India.

***Corresponding author:**
Gurudutt Joshi,
Department of Paediatrics,
Surat Municipal Institute
of Medical Education and
Research, Surat, Gujarat, India.

joshigurudutt@yahoo.com

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ABSTRACT

Objectives: Platelets play an important role in normal homeostasis and thrombus formation. They help in reducing vascular permeability, mediating inflammatory processes, promoting wound healing and host defence mechanisms. The aim of this was to estimate the prevalence of thrombocytopaenia, to categorise thrombocytopaenia according to the severity and to evaluate the role of thrombocytopaenia as a prognostic marker in patients admitted in PICU.

Materials and Methods: This was a prospective observational study over a period of 15 months. One hundred and eighty patients of age 1 month–17 years, critically ill, admitted in PICU or transferred from paediatric ward were enrolled. Those, who had thrombocytopaenia during admission or during PICU stay, were labelled as 'Thrombocytopaenia' group, while the remaining patients who did not have thrombocytopaenia were grouped as 'No thrombocytopaenia' group.

Results: The prevalence of thrombocytopaenia in PICU was 37.78% category wise, 35.29%, 33.82%, 19.12% and 11.76% of patients had mild, moderate, severe and very severe thrombocytopaenia, respectively. Mean duration of stay in PICU was more with severe and very severe thrombocytopaenia, followed by moderate and mild thrombocytopaenia, which was statistically significant (P = 0.00037). Mortality was higher in thrombocytopaenic group as compared to non-thrombocytopaenic patients expired, which was statistically significant (P = 0.001013).

Conclusion: The prevalence of thrombocytopaenia in this study was similar to other studies. Severity of thrombocytopaenia correlated well with the duration of PICU stay. Overall mortality was 22.22% in this study.

Keywords: Thrombocytopaenia, Prevalence, Paediatric intensive care unit

INTRODUCTION

The circulating life span of platelets is 10–14 days. Normal platelet count is 150–450 × 10^9/L. Decrease in platelet count below 150 × 10^9/L is labelled as thrombocytopaenia. Disseminated intravascular coagulation, increased destruction, reduced production, increased consumption and abnormal sequestration are mechanism of thrombocytopaenia. Thrombocytopaenia is a common complication in patients admitted to PICUs and may require transfusions.[1-5] The prevalence of thrombocytopenia varies in PICUs ranging from 13% to 60%.[6-9] Some of the drugs such as beta-lactams, linezolid, vancomycin and anticonvulsants such as phenytoin and valproic acid also cause decrease in platelet counts.[10-13] Implications of platelet count and its outcome have been studied in adult medical intensive care units but there are few studies and scarce

data available, as regards prevalence of thrombocytopaenia and its outcome in paediatric intensive care units (PICU), particularly in Indian setup; hence, this study was planned. Outcome of this study finding may add to the existing literature.

MATERIALS AND METHODS

This study was a prospective observational study conducted in PICU, over a period of 15 months (from 1 December 2018 to 29 February 2020). A study was approved by the 'Institutional Ethics Committee' and a written informed consent from the parent/guardian of enrolled patients was obtained. A total of 246 patients were enrolled, out of which 18 expired within 48 h of admission, 11 patients were discharged against medical advice (DAMA), 19 were transferred to paediatric ward after stabilisation of vitals within 48 h of PICU stay, 12 had deranged coagulation profile, five had received platelet transfusion in other setup before admission in PICU of our hospital and one patient had Glanzmann thrombasthenia, all these patients were excluded from this study. In addition, those patients, whose parents did not give consent, who had deranged coagulation profile, platelet function disorder and received platelet transfusion, were also excluded from the study. The remaining 180 patients were studied in detail and subjected to statistical analysis. Patients were studied for their entire duration of PICU stay (till discharge, transfer to paediatric wards, DAMA or death).

Sampling method

Platelet counts were performed as a part of routine investigations at the time of admission and as per treating physician but it was ensured that minimum of two investigations was done during the entire PICU stay. Any discrepancy in platelet count was counter confirmed by expert faculty. Patients with any of the platelet counts showing thrombocytopaenia during the duration of PICU stay were grouped into 'Thrombocytopaenic' group while the remaining patients who did not develop thrombocytopaenia during PICU stay duration were grouped into 'No thrombocytopaenic' group. Data were entered into predesigned pro forma. The lowest platelet count on admission or during PICU stay was used to grade the severity of thrombocytopaenia.

Statistical analysis

The sample size was calculated as per the average annual admissions in the PICU. The level of significance was 95%. The sample size calculated was 178 for the present study. Qualitative data were presented in the form of frequency (number) and percentage. Association between 'Thrombocytopaenia' and 'No thrombocytopaenia' with the qualitative variables was assessed by Chi-square test for 2×2 tables along with Yates correction and Fisher's exact test where Chi-square was not valid because of small counts. This analysis was done with the help of OpenEpi software. Quantitative data were represented by mean ± SD. For more than 2 rows and columns, R X C table for Chi-square testing was used for statistical analysis in OpenEpi software. Independent *t*-test and ANOVA test were applied for the evaluation of quantitative data wherever applicable. Odds ratio was applied for the evaluation of association between thrombocytopaenia and risk factors. Results were graphically represented where deemed necessary. Statistical analysis was done by MS Excel 2007, OpenEpi software (version 3.01) and SPSS 20 software. Graphical representation was done in MS Word 2007 and MS Excel 2007. $P < 0.05$ was considered statistically significant and confidence interval was at 95% confidence limit.

RESULTS

The classification of thrombocytopaenia[14] is as shown in [Table 1]. As shown in [Table 2], out of the 180 patients studied, 68 patients (37.78%) had thrombocytopaenia at least on a single occasion, while the duration of PICU stay, whereas 112 patients (62.22%) had platelet counts within the normal range. Fifty-nine patients from 68 patients had thrombocytopaenia on admission, whereas nine patients developed thrombocytopaenia during the PICU stay. The prevalence of thrombocytopaenia was observed to be 37.78% (i.e., 68 patients out of 180). Out of 180 patients, 92 patients (51.11%) are male and 88 patients are female (48.89%). Sex: Male predominance was observed with M: F ratio of 1.04:1. Age: The majority of the patients 64 (35.56%) were in the age group of 1–12 months, followed by 6–10 years and 11–15 years with 16 patients (16.11%) each. Mean age of the study population was 5.40 ± 5.94 years.

As shown in [Table 3], 68 patients had thrombocytopaenia, out of 180 patients enrolled, 24 patients (35.29%) had mild thrombocytopaenia, 23 patients (33.82%) had moderate thrombocytopaenia, 13 patients (19.12%) had severe thrombocytopaenia and 8 patients (11.76%) had very severe thrombocytopaenia.

Mean duration of PICU stay was 5.21 (~5) days and majority that is, 109 patients (60.59%) had <5 days of PICU stay. Ten patients (5.56%) had PICU stay of 5 days whereas 61 patients (33.89%) had PICU stay of more than 5 days, based on the mean duration of PICU stay, the study population was divided into three groups, with PICU stay lesser than, equal to and more than mean duration. As shown in [Table 4], the majority of thrombocytopaenic patients (51.47%) had PICU stay more than mean, while the majority of non-thrombocytopaenic patients (71.43%) had PICU stay of lesser than mean. Statistically significant difference ($P = 0.0003749$)

was observed with regard to the duration of PICU stay between the two groups. Hence, thrombocytopaenic patients required longer PICU stay duration as compared to non-thrombocytopaenic patients.

As shown in [Table 5], the mean duration of PICU stay for patients with thrombocytopaenia was 6.62 days, while it was 4.36 days in patients without thrombocytopaenia. Statistically significant difference was observed on comparison of mean PICU stay between the two groups (P = 0.00003585); hence, mean PICU stay was longer in thrombocytopaenic patients as compared to non-thrombocytopaenic patients.

As shown in [Table 6], mean PICU stay duration was more in severe thrombocytopaenia (10.15 days) followed by very severe thrombocytopaenia (8 days). There was statistically significant difference (P = 0.00037) observed on comparison of mean PICU stay with severity of thrombocytopaenia. Hence, the mean PICU duration is more for patients with severe and very severe thrombocytopaenia as compared to patients with mild and moderate thrombocytopaenia. No statistical test could be applied as it does not meet Cochrane criteria for Pearson Chi-square testing between severity of thrombocytopaenia and gender as well as age.

[Table 7] reflects that overall mortality observed in this study was 22.22% (40 patients out of total 180 patients studied). From the 140 patients (77.78%) that survived during the period of this study, 129 patients (71.67%) were given discharge after the completion of treatment whereas 11 patients (6.11%) had taken DAMA due to varied reasons such as personal, social or economical issues after being vitally stable and transferred to paediatric ward. Patients who had taken DAMA during the course of treatment and vitally unstable have been excluded from this study. Only those patients who had taken DAMA after being vitally stable and transferred to paediatric ward have been included in the study. Gender and age were not found to be statistically significant, as risk factors for thrombocytopaenia, as p value for both was 0.7019 and 0.6458, respectively.

[Table 8] depicts that 35.29% of thrombocytopaenic patients expired, while only 14.29% of non-thrombocytopaenic patients expired. Statistically significant difference was observed on comparison of mortality and thrombocytopaenia. Hence, mortality was more in patients with thrombocytopaenia as compared to patients without thrombocytopaenia. When gender was considered as risk factor for mortality in thrombocytopaenic patients, it was found to be statistically insignificant as P = 0.3858. No statistical test can be applied, to age, as a risk factor for mortality in thrombocytopaenic patients, as it did not meet Cochrane criteria for Pearson Chi-square testing.

Table 1: Grading of thrombocytopaenia.

Grade of thrombocytopaenia	Platelet counts (µL)
Mild	100,000–150,000
Moderate	50,000–100,000
Severe	20,000–50,000
Very severe	<20,000

Table 2: Prevalence of thrombocytopaenia.

Thrombocytopaenia	Number	Percentage
Present	68	37.78
Absent	112	62.22
Total	180	100

Table 3: Severity of thrombocytopaenia.

Severity of thrombocytopaenia	Number	Percentage
Mild	24	35.29
Moderate	23	33.82
Severe	13	19.12
Very severe	8	11.76

Table 4: Duration of PICU stay as a risk factor for thrombocytopaenia.

Duration of PICU stay	Number	Percentage	Thrombocytopaenia				Total
			Present		Present		
			Number	Percentage	Number	Percentage	
<5 days	109	60.56	29	42.65	80	71.43	109
5 days	10	5.55	4	5.88	6	5.36	10
More than 5 days	61	33.89	35	51.47	26	23.21	61
Total	180	100	68	100	112	100	180
Chi-square tests		**Value**		**df**		***P*-value**	**Association**
Pearson Chi-square		15.78		2		0.0003749	Significant

Mean duration of PICU stay of the study population was 5.21±3.63 days

Table 5: Comparison of mean duration of PICU stay between thrombocytopaenic and non-thrombocytopaenic group.

Thrombocytopaenia	Number of patients	Mean±SD	Minimum	Maximum
Present	68	6.62±4.04	2	16
Absent	112	4.36±3.07	2	22
Total	180	5.21±3.62	2	22

Independent *t*-test	Value	df	Lower limit	Upper limit	Mean difference	*P*-value	Association
Equal variance	4.24	178	1.208	3.311	2.26	0.00003585	Significant

Table 6: Association of mean duration of PICU stay and severity of thrombocytopaenia.

Severity of thrombocytopaenia	No. of patients	Mean PICU stay±SD	Min	Max
Mild	24	3.96±3.97	2	12
Moderate	23	6.91±4.07	2	13
Severe	13	10.15±4.26	3	16
Very severe	8	8.00±4.05	4	12

ANOVA test	Value	df	Mean square	*P*-value	Association
Equal variance	348.97	3	116.325	0.00037	Significant

Table 7: Outcome of patients.

Final outcome	Total no. of patients	Percentage
Survived	140	77.78
Expired	40	22.22
Total	180	100.00

As shown in [Table 9], the mean PICU stay duration is longer in expired thrombocytopaenic patients as compared to thrombocytopaenic patients who survived and these data were statistically significant ($P = 0.000029$). Maximum PICU stay was longer in expired thrombocytopaenic patients as compared to survived ones. Hence, longer PICU stay was associated with mortality in thrombocytopaenic patients and may be used as a mortality predictor in thrombocytopaenic patients.

DISCUSSION

Prevalence

The prevalence of thrombocytopaenia observed in various studies ranges from 25 to 60%. In this study, the prevalence was 37.78%. This is similar to the results shown in the studies conducted by Sah *et al.*[15] and Kaur *et al.*[1] where the prevalence of thrombocytopaenia was 34% and 32.36%, respectively. Relatively higher prevalence was observed in the studies conducted by Divecha *et al.*[8] (60.3%), Yilmaz *et al.*[6] (59.57%) and Mussa *et al.*[16] (44.61%), respectively, while relatively lower prevalence was observed in the studies conducted by Krishnan *et al.*[17] (25.3%) and Agrawal *et al.*[7] (25%). The difference in the prevalence of thrombocytopaenia may be attributed to the varying inclusion criteria of the different studies. Moreover, patients with burns have a separate ICU and hence not included in the present study. Almost all above studies had also male preponderance.

Age

Maximum age range was 1 month–18 years in the study of Mundkur *et al.*[18] The mean age of the patients in the present study was 5.4 years which is similar to the studies conducted by Mittal *et al.*[19] and Mussa *et al.*[16] The range of age groups of the study population in this study was 1 month–17 years, which is similar to that of the study by Mundkur *et al.*[18] who had included patients from 1 month to 18 years of age. The median age observed in our study was 36 months (3 years), which is similar to the study by Agrawal *et al.*[7] (2008), where a median age was 32 months. Yilmaz *et al.* (2013)[6] conducted a study which showed the median age of 24.

Severity of thrombocytopaenia

In this study, maximum patients 24 out of total 68 thrombocytopaenic patients that is, 35.29% had mild thrombocytopaenia followed in decreasing order by moderate thrombocytopaenia (33.82%), severe thrombocytopaenia (19.12%) and very severe thrombocytopaenia (11.76%). Similar results were observed in the study conducted by Sah *et al.*[15] where maximum (41.7%) patients had mild thrombocytopaenia (platelet count $<150 \times 10^9$/L) followed by 32.3% of patients with moderate thrombocytopaenia (platelet count $<100 \times 10^9$/L) and 26.4% of patients with severe thrombocytopaenia (platelet count $<50 \times 10^9$/L). Studies conducted by Mundkur *et al.*[18] and Kaur *et al.*[1] who showed higher prevalence of severe thrombocytopaenia 51% (platelet count $<50 \times 10^9$/L) whereas the study by Yilmaz *et al.*[6] showed lower prevalence (7.45%) of severe thrombocytopaenia as compared to our study. Thus, there is varying prevalence of severity of thrombocytopaenia.

Table 8: Association of thrombocytopaenia with mortality.

Outcome	Thrombocytopaenia		Total
	Yes (*n*=68)	No (*n*=112)	
Survived			
No.	44	96	140
%	64.71%	85.71%	77.78%
Expired			
No.	24	16	40
%	35.29%	14.29%	22.22%
Total			
No.	68	112	180
%	100.00%	100.00%	100.00%

Chi-square tests	Value	df	*P*-value	Association
Pearson Chi-square	10.8	1	0.001013	Significant

Table 9: Association of mean PICU stay duration with mortality in thrombocytopaenic patients.

Outcome	Number of patients	Mean PICU stay duration Mean±SD	Min.	Max.
Expired	24	9.58±4.04	2	16
Survived	44	5.00±4.01	2	12
Total	68	6.62±4.04	2	16

Statistical test	Value	df	Mean difference	*P*-value	Association
Independent t-test	4.48	66	0.1464	0.000029	Significant

Duration of PICU stay

In this study, the mean duration of PICU stay was found to be 5.21 (±3.63) days. The majority of patients (60.56%) had PICU stay duration of <5 days whereas 5.55% had PICU stay duration of 5 days and 33.89% had more than 5 days of PICU stay. The study conducted by Mundkur *et al.*[18] who showed that the median duration of PICU stay in mild and moderate thrombocytopaenia was 4 days and in severe thrombocytopaenia was 3 days. The median duration of PICU stay was 8 days (3–120 days) in the study by Yilmaz *et al.*[6] In the study by Mussa *et al.*,[16] PICU stay duration was divided into <7 days, 7–14 days and >14 days with 56.2%, 25.4% and 18.5% of study population, respectively. Agrawal *et al.*[7] found that 99 (71.1%) patients had PICU stay duration of <7 days while 20 (14.5%) had more than 14 days of PICU stay and 19 (13.8%) PICU stay of 7–14 days. The duration of PICU stay would depend on the type of diagnosis of the patients admitted in the PICU, treatment protocols and the outcome.

Duration of PICU stay and thrombocytopaenia

In this study as well as studies by Yilmaz *et al.*,[6] Mussa *et al.*,[16] Agrawal *et al.*[7] and Krishnan *et al.*,[17] longer duration of stay was observed in thrombocytopaenia group as compared to non-thrombocytopaenia group, which was statistically significant whereas in a study of Mittal *et al.*,[19] this difference was insignificant.

Outcome

Mortality was 22.22% in this study, which was comparable to Sah *et al.*[15] (26%), Mittal *et al.*[19] (20%) and Kaur *et al.*[1] (19.64%), whereas it was 37.2% and 53.07% in Yilmaz *et al.*[6] and Mussa *et al.*[16] study. The difference may be attributed to the different diagnosis of the patients and admission criteria in different studies.

Thrombocytopaenia and mortality

In this study, 35.29% of thrombocytopaenic patients expired while only 14.29% of non-thrombocytopaenic patients expired and this was statistically significant. Similarly, statistically significant association between mortality and thrombocytopaenia was observed in various studies as shown in table below. Kaur *et al.*[1] and Mittal *et al.*[19] observed that mortality among thrombocytopaenic and non-thrombocytopaenic patients was similar to this study. Higher mortality was observed among thrombocytopaenic patients in the studies by Sah *et al.*,[15] Yilmaz *et al.*,[6] Mussa *et al.*[16] and Agrawal *et al.*[7] while lower mortality was seen among thrombocytopaenic patients in studies by Mundkur *et al.*[18] and Krishnan *et al.*[17] Sah *et al.*[15] observed that there were 18 times more risk of mortality among thrombocytopaenic patient compared to non-thrombocytopaenic patients with odds ratio 18 at 95% CI. Mortality including this study was statistically significant in thrombocytopaenic group as compared to non-thrombocytopaenic group in all studies.

CONCLUSION

The prevalence of thrombocytopaenia in the PICU observed in this study was 37.78%, of which mild thrombocytopaenia was predominant (35.29%). Male preponderance was observed in this study. Duration of stay in PICU correlated well with a severity of thrombocytopaenia, also thrombocytopaenic patients had statistically higher risk of death; hence, thrombocytopaenia may be considered as an important risk factor for mortality.

Limitation of the study

Patients with burns could not be recruited in this study, as there was separate burns ward in the institute. Association of risk factors with a severity of thrombocytopaenia because could not be correlated as they were not meeting Cochrane criteria for statistical testing. The role of thrombocytopaenic drugs in causing thrombocytopaenia was not assessed.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Karnataka Paediatric Journal

Original Article

A non-invasive novel approach for managing digestive tract foreign body ingestion in children

Sayanthan Balasubramaniam[1], Sanjaya Abeygunasekara[2], Ganeshrajah Arunasalam[3], Thiruvarangan Suwaminathan[1]

[1]Department of Surgery, University of Jaffna, Jaffna, [2]Department of Paediatric, Lady Ridgeway Hospital, Colombo, [3]Department of Peadiatric, Teaching Hospital Batticaloa, Batticaloa, Sri Lanka.

***Corresponding author:**
Sayanthan Balasubramaniam, Department of Surgery, University of Jaffna, Jaffna, Sri Lanka.

srisayan@gmail.com

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ABSTRACT

Objectives: The phenomenon of foreign body ingestion (FB) is considered a common scenario in children's tertiary care clinical settings. This study aimed to assess the sociodemographic factors of ingested FB, and its details and find the efficient clinical outcomes of a novel non-invasive interventional approach for removing FB in children.

Material and Methods: This was a prospective study of 55 patients in a tertiary care centre, Sri Lanka for 1 year from 2019. The univariate, bivariate analysis, and the Chi-squared test were used to check the relationship between two categorical variables as this study dataset comprises more than 50 observations, where 5% was used as the significance level.

Results: This study's mean age was 5.18 ± 3.1 years and the median 5 years. The higher number of ingested FB was metal (88.5%) among this coin (33.3%) recorded the highest contribution and round shape was 62% whereas the ratio between sharp edge and none sharp edge was 1:4. A greater number of children both males (58.3%) and females (30.6%) were managed spontaneously to pass the FB through stool while vomiting (2.78%) was observed only in males. In comparison, the endoscopy removal cases were female (5.56%) and their mean age was 7.7 years.

Conclusion: There are a number of studies that claim that the management of FB ingestion relatively depends on children's age, developmental stage, the type of the ingested object, and clinical presentation. However, our study contends that the majority of FB ingestion can be moved spontaneously through stool by applying the non-invasive therapeutic approach without causing clinical complications.

Keywords: Foreign body ingestion, Children, Endoscopy, Guidelines

INTRODUCTION

The scenario of foreign body (FB) indigestion is considerably a significant problem in children because they are very keen to explore the environment by keeping the objects in their mouths. Unfortunately, a number of these tiny objectives can be unintentionally swallowed, and eventually, this has resulted in increasing parental anxiety.[1] The gender distribution of FB ingestion is relatively equal between boys and girls as well as a higher number of incidents is noted in the age ranging from 6 months to 3 years.[2] The majority of swallowed FBs are eliminated naturally through the gastrointestinal tract (GI) without causing any clinical complications although endoscopic and surgical approaches are required only in a few cases.[1,3] According to a recent research study, 80%–90% of particles were passed naturally through the GI tract without causing any complications while 10%–20% were removed by endoscopic procedures and there was only 1% required open surgery.[4] Because in some ingested phenomena, a foreign body cannot easily

move through the part of the GI tract such as the pylorus, stomach, duodenum, and ileocecal valve.[2,5]

The common type of swallowed FBs is radiopaque including coins, screws, tiny magnets, safety pins, nails, plastic buttons, and button batteries though the radiolucent object like food particle impaction is to be considered in the ingested management.[4] The digestive tract FBs are frequently asymptomatic and ingestion likely mimics other conditions such as cough, vomiting, sore throat, and chest discomfort or abdominal pain.[6] The clinical diagnosis of FB ingestion in children is often challenging because children are unable to express the incidents and clinicians should not rely on it. However, the history of eyewitness accompanied adults may useful although usually more than 3 years of old children can give the history of ingestion themselves.[2] Most of the time FB ingestion is transiently discomfort and later becomes symptomless or can be presented with mild irritation, even rarely causing a life-threatening problem.[7] Some factors influence the necessity of emergency removal of FBs including the type, shape, size and site.[8] It is important to develop a comprehensive approach to the early recognition and timely management of ingested FBs.[2,9] Moreover, to reassure the anxiety of the parents and children, it is essential to have successful alleviation management to avoid developing complications regarding ingested cases.[10] The primary objective of this study is to assess the sociodemographic factors of ingested FB, its details as well as identify the efficient management of swallowed FBs and the key factors which influence the FBs removal procedure. As a result, this study will help to establish the guideline to manage the FBs ingestion in children and help to initiate the awareness programme in Sri Lanka.

MATERIAL AND METHODS

This study was conducted as a prospective analytical study in a tertiary care centre, in Sri Lanka for 1 year from 2019. This study aims to assess the particular aspects of FB ingestion including sociodemographic factors, and details of FB, and find the efficient clinical outcomes of a novel non-invasive interventional approach. Moreover, assessing the factors that influence the ingested FB removal in children, who were admitted to Lady Ridgeway Hospital, Sri Lanka. The novel non-invasive interventional approach combined with lactulose syrup, liquid paraffin syrup, domperidone syrup, and ducolax suppository according to the patient's weight in addition to the victim was asked to the right lateral sleep. This study recruited 55 ingested children, who were documented as an index suspicion of FB swallowing while the exclusion criteria were aspiration of FB and were not given informed consent to participate in this study.

The data extraction form was used to collect sociodemographic, details of FB, clinical presentations, and therapeutic procedures from patients' records, and additional information such as when, where, and who was accompanied with children were taken from the affected children and/or guardians. In this study, the setting was a tertiary care centre, the patients also were referred to this hospital's emergency treatment unit from other community hospitals, where the endoscopy service was limited. Initially, all the patients underwent to a plain thoracic-abdominal radiological image within the 1st h of their admission regardless of the history of the incident and clinical symptoms. In some cases, the upper GI tract endoscopy was done by the same clinicians because some of the ingested FBs are radiolucent as receiving the negative X-ray of ingested materials. To achieve the study objectives initially, the descriptive analysis was carried out using the statistical software Statistical Package for the Social Sciences (version 26) to know the characteristics and distribution of variables and identifies the relationship between two variables. This descriptive analysis was conducted through two steps including univariate and bivariate analysis. The Chi-squared test was used to check the relationship between two categorical variables as this study dataset comprises more than 50 observations, where 5% is used as the significance level.

RESULTS

According to the histogram of age, children's age ranged from 1 to 13 years whereas the mean age was 5.18 ± 3.1 years and the median was 5 years. Overall, ages were distributed as skewed to the right. Among this study participant, the gender ratio between boys and girls was 3:2 [Figure 1]. The majority of this study participant was from the Colombo district (47.3%) while the following common residential regions were Gampaha (27.7%) and Kalutura (14.6%). A larger number of swallowed children (n = 52) had appropriate developmental stages but only a few victims (n = 3) had a developmental

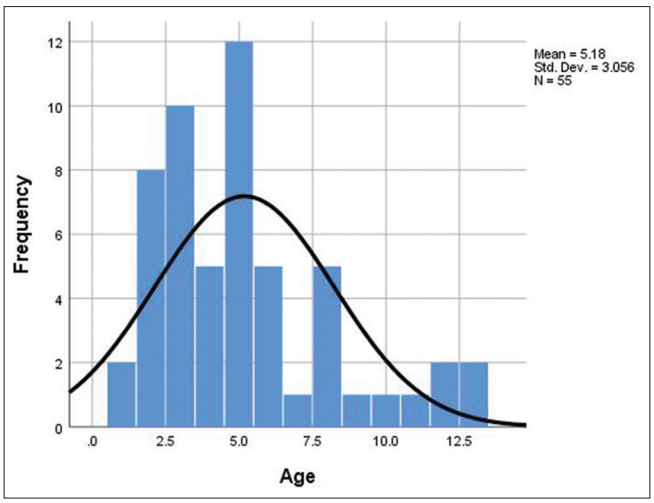

Figure 1: Histogram of patients' age.

delay. The higher number of ingested FB was metal (88.5%) although rubber, glass, and food particle accounted for only a small proportion 3.8%, 1.9%, and 1.9%, respectively. Among the larger number of metal FB ingestion, coins amounted to the highest proportion, at 33.3% while button battery was the second higher incident (29.4%). There were 13.7% and 5.8% recorded nail and jewellery items, respectively. It was noticeable that the largest proportion of shapes was round (62%) whereas both spherical and tubular were approximately one-tenth of round shape cases. However, there were 29% cases with irregular shape FBs ingestion. In addition, this study found that a larger proportion of swallowed FBs had no sharp edge as the ratio between sharp edge and non-sharp edge was 1:4. The greatest numbers of FBs were found in the stomach (70.7%) although the intestine was 17.1% and the upper and lower part of the oesophagus was 2.4% and 9.8%, respectively.

This study identified that 62.9% of incidents occurred in the presence of adults despite the majority being passive (55.8%). This study found that the largest number of incidents (88.8%) happened at home while approximately 10% took place at pre-school and 7.4% occurred outside the home. Almost 98% of swallowed cases had been investigated through plain radiological images only 1.9% was undergone endoscopic examination. However, the majority of cases (90.3%) presented with asymptomatic of indigestive although very limited incidents (9.6%) were associated with clinical presentation of vomiting, sore throat, and cough. This study found that 88.8% of FB ingestions were passed spontaneously with a stool while 8.3% of cases required endoscopy removal but only 2.78% swallowed FBs eliminated naturally with vomiting [Figure 2]. However, none of the cases of this study had complications after the removal of FBs although greater numbers of cases (92.1%) were discharged within a day of admission to the hospital. In addition to that, it was noticed that a greater number of children both male (58.3%) and female (30.6%) were managed spontaneously to pass the FB with stool. All the cases treated with naturally vomiting (2.78%) were male; in comparison, all the endoscopy removal cases were female (5.56%). This study found that when the FB was located in the upper part of the oesophagus and intestine patients were only managed spontaneously with stool [Figure 3]. The following summarizes the factors with corresponding *P*-values, which show the statistically significant relationship with the procedure when the Chi-squared test was carried out [Table 1].

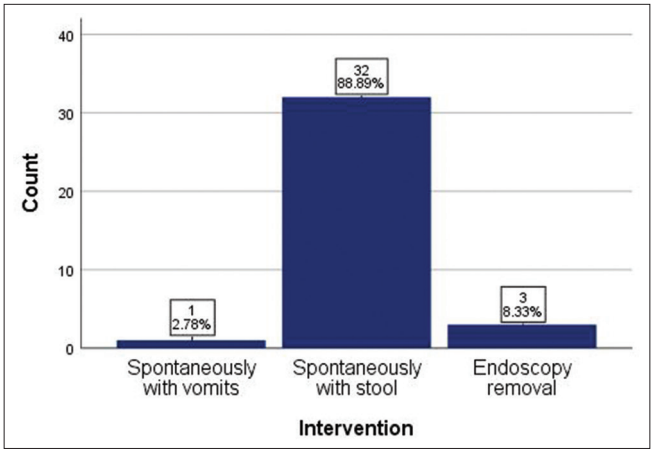

Figure 2: Intervention approach of foreign body removal.

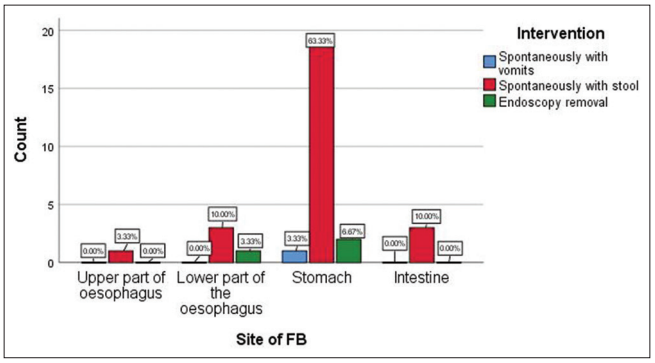

Figure 3: Intervention approach and foreign body location in the gastrointestinal tract.

Table 1: Association between procedure and following factors.

Variables	*P*-value
Shape of FB	0.000
Sharpness of FB	0.024
Symptoms after incident	0.000
Investigation method	0.003

DISCUSSION

The FB ingestion is a significant incident in paediatric clinical practice, most events occur in children ages ranging from 6 months to 3 years.[11] In our study, this showed that children's age ranged from 1 to 13 years whereas the mean age was 5.18 ± 3.1 years and the median was 5 years. This study participant's gender distribution between boys and girls was 3:2. These similar findings are consistent with other gender distribution reports related to FB ingestion a research study showed slightly male predominance.[3,4] It is largely acknowledged that the high prevalence of FB ingestion is identified in children because of their exploratory habits despite involving the gender difference between males and females.[12] The majority of this study's participants were represented from the district where this study setting is located. This may help to come up with a postulation that FB ingested children were directly brought to the children's specialty hospital rather than making delayed by admitting to other hospitals as the children accompanied by adults have

a better awareness of the children's care. However, this study found that 62.9% of incidents occurred in the presence of adults despite the majority being passive (55.8%).

A Romanian study claimed that in the clinical presentation consideration, common complaints were abdominal pain and vomiting 55.73% and 34.42%, respectively, also 29.5% of cases were asymptomatic ingested children.[1] However, in our study, the majority of cases (90.4%) presented with asymptomatic of indigestive FB with very limited incidents (9.6%) associated with clinical presentation of vomiting, sore throat, and cough. A similar result of a high prevalence of asymptomatic ingested incidents was reported in a number of other studies.[2,13] Our study suggests that the manifestations of indigested FB clinical features are depended on the type of FBs as a statistically significant relationship (P = 0.039) was found between types of FB and symptoms. In addition, factors such as sharpness of FB (P = 0.024), investigation method (P = 0.003), and symptoms after swallowing FB (P = 0.000) also showed a statistically significant relationship with the procedure, which was identified through the Chi-squared test. Moreover, our study included a wider range of ingested objects such as coins, button batteries, nails, jewellery, and unidentified objects though the most frequently swallowed FB was coins this similar finding was reported in another study (33.3%).[14] Furthermore, our study noticed that the ingestion of button batteries had the second higher (29.4%) incidence in children because this might be the age-specific preference as they frequently use toys in their early childhood stages.[13] However, in our study, all ingested button batteries were managed to pass spontaneously with stool despite considering a greater number of studies claim that button batteries should be removed immediately. Because of the high risk of sparking between the anode and cathode of the battery by the soft tissue of the GI tract, as well as, the high concentration of HCL in the stomach might cause degradation of the battery subsequently developing poison due to the chemical containing battery.

A retrospective study in a similar tertiary care clinical setting assessed the association between site and size of ingested FBs also investigated the relationship between the size and the clinical features. They stated that the expected results could not be objectified probably due to the heterogeneity of age distribution among the participated subjects.[15] In our study, participants had the similar heterogeneous distribution of age thus we could not objectify the association between the size of FBs and site as well as the clinical features. The plain radiological image is an essential diagnostic tool in swallowed FB cases in the main initial investigation approach.[16] In our study, almost 98% of swallowed cases had been investigated through plain radiological images only 1.9% had been examined by endoscopy although a number of studies reported X-ray identification that ranged from 63.1% to 96.4%.[17,18] Our study tends to agree with other authors who claimed that the optimal clinical procedure for removing the FB is largely dependent on many factors including the children's age, the clinical features, type, shape, location, and sharpness of the FB.[19] The drawn clustered bar chart between interventional procedure and shape of FB indicates that a high percentage of children treated spontaneously with the stool were swallowed round shape of FB (64.7%) while it was only 5.9% spherical shape of FB and there were no cases in a tubular shape. Moreover, a statistically significant relationship between procedure and shape of FB was identified (P = 0.000) through the Chi-squared test. When considering the age factor, the average age of endoscopy removal was 7.7 years compared to the average age of patients in other procedure methods such as spontaneously with stool (5 years) and spontaneously with vomiting (3 years). Furthermore, all the cases treated with endoscopy removal (8.3%) consisted of only normal developmental stage and all were metal FBs. Furthermore, it was found that most of the asymptomatic patients (88.9%) were managed spontaneously with stool and among the symptomatic patients (9.6%) only 5.6% were managed by endoscopy removal. Therefore, endoscopy removal could be suggested for the normal developmental stage of children at approximately 7 years of age and incidents of metal FB ingestion with asymptomatic cases. Furthermore, an endoscopy therapeutic method is quite expensive and it requires general anaesthesia before the procedure but this procedure is more challenging and potential risk for the younger population. Considering the study limitations, this study participant's age had a wider range of 1–13 years as a result of the heterogeneous distribution of age, we could not objectify the association between the size of FBs and location additionally, a similar problem has been encountered for assessing the relationship between FBs and clinical features of FB ingestion. Moreover, in our study, the majority of ingestion FB type was metal; however, other type of FBs was very limited thus we are unable to evaluate the association between other types of FB with our therapeutic procedure.

CONCLUSION

FB ingestion is a potentially serious problem that peaks at a younger age. There are a number of studies that claim that the management of this pathology relatively depends on the patient's age, developmental stage of children, the type of the ingested objects, and the clinical presentations. However, our study findings contend that the majority of ingested FBs can be passed spontaneously through stool by applying the non-invasive therapeutic approach without causing clinical complications despite considering other factors such as age, gender, and type of FBs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Karnataka Paediatric Journal

Case Report

Incontinentia pigmenti with ocular, cutaneous and CNS manifestation

Neethu Helan Varghese[1], Venugopalan Nettiyath[1]

[1]Department of Paediatrics, DM WIMS Medical College, Meppadi, Kerala, India.

***Corresponding author:**
Venugopalan Nettiyath,
Department of Paediatrics,
DM WIMS Medical College,
Meppadi, Kerala, India.

dr.neethuhelan@gmail.com

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ABSTRACT

Incontinentia Pigmenti (IP) is an uncommon X-linked genodermatosis, with an estimated prevalence at birth of 0.7/100,000, caused by mutations in the NEMO gene. Ectodermic and mesodermic origin of tissue is seen in this systemic disease including cutaneous tissue, teeth, eyes, and the central nervous system. Herein, we present a case of a female newborn with inflammatory vesiculopustular lesions all over the body. This baby also had ocular, and CNS manifestations as well. The importance of a detailed diagnostic workup for the newborns with pustular skin disease has been highlighted in this case. IP is a rare, x-linked dominant genodermatosis with the involvement of multiple organs. Dermatological abnormalities are the most prominent manifestation. The diagnosis is based on the clinical findings of skin lesion brain imaging and biopsy. The skin lesions do not require specific treatment and prognosis depend on other organ involvement.

Keywords: Bloch-Sulzberger syndrome, Incontinentia pigmenti, Newborn, Pustular skin lesions, X-linked, retinal detachment

INTRODUCTION

Incontinentia pigmenti (IP), first described by Garrod in 1906, after that Bloch and Sulzberger defined this disorder in 1926 and 1928, respectively, is a multisystem disorder inherited in an X-linked dominant fashion with lethality in males. The skin lesions are diagnostic and occur in four stages, all of which may not be seen in one patient. IP can have involvement of other systems which include the central nervous system seen as intellectual disability, microcephaly, stroke, and seizures. The ocular changes are ischemia of the peripheral retinal field, retinal dysplasia, retinal detachment, pigment retinopathy, and retrolental dysplasia. The musculoskeletal system can have hemivertebrae, kyphoscoliosis syndactyly, and hemiatrophy. Dental abnormalities include hypodontia, microdontia, and dysplasia. Hair may be coarse, wiry, lusterless with alopecia.[1]

Transmission of the disease in females by a lionization results in functional mosaicism of X-linked genes. Vesicular stages of IP are present at birth or develop in the first few weeks of life in most cases. The characteristic stages are blistering (from birth to about 4 months of age) followed by verrucous plaques (for several months), swirling macular hyperpigmentation (from about 6 months and persist during childhood and usually fade by adolescence) and in later stages linear hypopigmentation (that develops during adolescence and early adulthood which persists indefinitely).[2]

Hair, nail, and dental anomalies are often manifested during infancy. Permanent neurologic (Cognitive delays/mental retardation) and ophthalmologic sequels develop during early infancy so that patients would have retinal vascular abnormalities predisposing to retinal detachment in early childhood but strabismus and cataract are occasionally seen. Breast, skeletal, and structural anomalies are sometimes rarely seen in patients.[2]

CASE REPORT

Female baby born by normal vaginal delivery to Primi mother with third degree consanguineous marriage, no antenatal issues, no history of fever with rash anytime during pregnancy or delivery nor any history of contact with anybody having rash. She presented with a history of rash since day 1 of life. Rash was in the form of fluid-filled vesicles over the upper limb, lower limb, and trunk. Day 5 of life baby developed poor feeding with intermittent sucking and reduced activity. Day 8 of life baby had one episode of seizure in the form of rhythmic contractions of both upper and lower limbs which lasted for few seconds. LP done was normal. Sepsis screen done was negative. Neurosonogram showed cerebral edema. CBC showed eosinophilia and CRP, VDRL, and HSV PCR was negative [Figure 1a-d].

Dermatology consultation was done followed by Punch biopsy which showed mild hyperkeratosis with subcorneal vesicle containing plasma, neutrophils, and eosinophils. The dermis shows perivascular infiltrates of few eosinophils [Figure 2a and b].

MRI brain reported multiple patchy foci of diffusion restriction in the subcortical white matter of both frontal, right parietal regions and deep white matter of right frontal region appearing hyperintense on FLAIR- subacute infarcts. Linear foci of T1 hyperintensity in the subcortical and deep white matter of both cerebral hemisphere-hemorrhages. Few irregular cystic areas in bilateral parietal left frontal subcortical white matter. Diffuse altered signal intensity of white matter. Corpus callosum appears hypoplastic with findings suggestive of IP [Figure 3a and b].

Ophthalmology evaluation of fundus in the early neonatal period showed patchy retinal hemorrhages. On subsequent follow-up at 9 months showed evolving Retinal detachment with secondary glaucoma of the left eye.

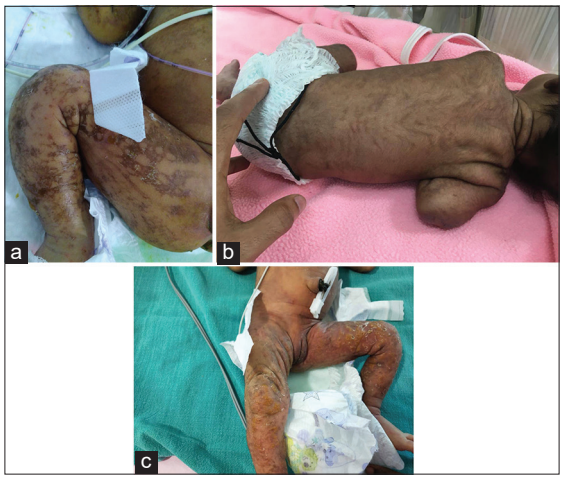

Figure 1: (a) Whorl pattern. (b) Skin lesions along lines of Blaschko. (c) Vesicopustular eruptions.

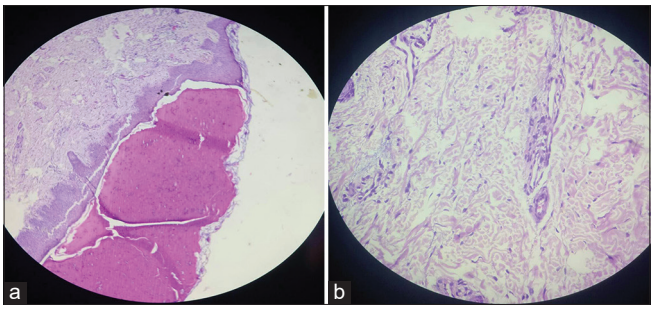

Figure 2: (a and b) Histopathology.

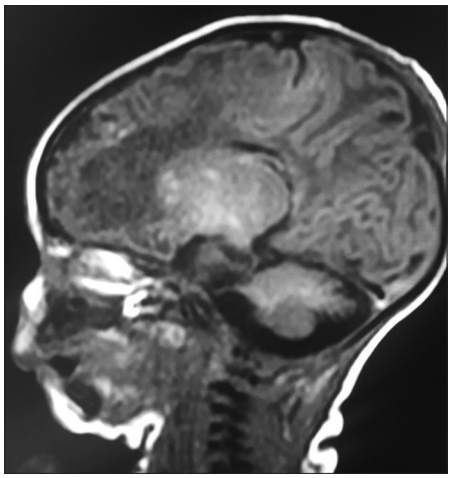

Figure 3: MRI ,corpus callosum agenesis.

DISCUSSION

The IP as an X-linked dominant disorder is lethal in males.

IP is a rare multisystem disease, which is characterized by the abnormalities of the tissues and organs which are embryonically derived from the ectoderm and neuroectoderm.[3] The pigment melanin that normally lies in the melanocytes of the basal epidermal layer is seen in the superficial layer in the IP. The skin changes in IP are the major criteria for diagnosis of this disorder. These variations typically occur at birth or during the 1st weeks of life and continue to adulthood while distributing along Blaschko's lines which were typical in our case.

	System	Evaluation and timing	Expected findings
Neonatal period	Ocular	Fundoscopy	To evaluate the optic nerve, macula, and far periphery
	CNS	MRI brain	Ischemic changes, stroke
	Cardiac	Echo	Pulmonary hypertension
	Skin	Biopsy	Eosinophilia
	Genetics	Genetic testing	x-linked inheritance
Infancy through age 3 years	Ocular	Fundoscopy: Every month until 4 months 4 months-1 year: every 3 months 1 year-3 year: Every 6 months Annually lifetime	Retinal detachment
	Dental &speech	Examination at 6 months	Hypodontia, conical teeth, affected speech
	CNS	Developmental assessment and EEG if seizure occurs	Developmental delay
	Genetics	Evaluated at puberty and prenatally	Each pregnancy will carry a 50% risk of receiving the mutation

The diagnostic criteria for IP was proposed by Landy and Donnai in 1993. In our case, baby was born to parents with third-degree consanguinity, but no family history of any genetic conditions was reported.[4]

The histopathological findings in our patient were compatible with the early phase. The skin biopsy report showed an eosinophilic predominance which is a typical characteristic of IP.

The central nervous system is the most affected system after the skin in IP patients, which is about 10–40% of the cases. Central nervous system involvement can have a major impact on the patient's quality of life, even though the baby had significant changes in MRI she had attained early milestones on time. There has been an early study which showed reversible brain changes in patients with IP.

In 30-70% of the IP patients coular diseases such as strabismus, microphthalmia, and pigmentary retinal changes are seen. Vision loss has been associated with vascular occlusions, secondary extraretinal neovascularization, fractional retinal detachment, and foveal hypoplasia. In our patient routine screening in the neonatal period showed retinal hemorrhage, hence regular follow-up was arranged for fundoscopy wherein early detection of retinal detachment and secondary glaucoma was made.

Hair abnormalities in IP (e.g., alopecia, sparse hair, as well as hypoplasia of eyebrows and eyelashes), had been reported in 28–38% of the patients. Scarring alopecia of the vertex is the most common manifestation of hair involvement.

The IP can also involve nails and lead to such abnormalities as dystrophy and fibromas. Nevertheless, no hair or nail involvement was observed in our case.

The diagnosis of IP is based on the clinical features. Differential diagnosis including neonatal herpes simplex infection, congenital syphilis, impetigo, neonatal bullous dermatoses, and autoimmune blistering were considered. Since the spontaneous resolution of the lesions usually occurs, the skin lesions of IP do not require specific treatment.

As discussed IP had a multisystem involvement, with cutaneous, CNS, and ocular manifestations. Hence a multidisciplinary approach is required for management. It has been hence evident that regular ophthalmologic follow-up is also essential in those cases with IP for timely detection of vascular changes and prompt treatment. Successful use of dexamethasone has been reported in one highlighted case to treat seizures supports the idea that inflammation is a part of the process. Unfortunately, a treatment protocol using dexamethasone in this population is difficult to establish given the very small numbers of infants born with the condition.[5] More of cases reported and research is required in this regard for an early detection, screening, and genetic counseling.

Recommendations for evaluation and follow-up of IP

CONCLUSION

As discussed IP had a multisystem involvement , with cutaneous,CNS and ocular manifestations. Hence a multidisciplinary approach is required for management.It has been hence evident that regular ophthalmologic followup is also essential in those cases with IP for timely detection of vascular changes and prompt treatment . Successful use of dexamethasone has been reported in one highlighted case to treat seizures supports the idea that inflammation is a part of the process.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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Karnataka Paediatric Journal

Case Report

Thiamine-responsive megaloblastic anaemia syndrome – A case report

S. N. Shubha[1], Sudha Rudrappa[1]

[1]Department of Pediatrics, Mysore Medical College and Research Institute, Mysore, Karnataka, India.

***Corresponding author:**
S. N. Shubha,
Department of Pediatrics,
Mysore Medical College and
Research Institute, Mysore,
Karnataka, India.

snshubha7@gmail.com

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ABSTRACT

Thiamine is a water-soluble vitamin which is helpful for tissue growth and development. Thiamine-responsive megaloblastic anaemia (TRMA), also known as Rogers syndrome, is caused by the mutation of a gene SLC19A2 which encodes for a thiamine transporter protein. TRMA is characterised by the triad of megaloblastic anaemia, progressive sensorineural hearing loss and diabetes mellitus. The onset of megaloblastic anaemia is between the extremes of infancy and adolescence, which can be corrected with pharmacological doses of thiamine. Progressive sensorineural hearing loss is generally early in onset, irreversible and may not be prevented by thiamine treatment.

Keywords: Thiamine-responsive megaloblastic anaemia, SLC19A2, Diabetes mellitus, Sensorineural hearing loss

INTRODUCTION

Thiamine-responsive megaloblastic anaemia syndrome (TRMA) is a rare autosomal recessive disorder.[1] It is characterised by megaloblastic anaemia, diabetes mellitus and sensorineural hearing loss. Mutation in the gene SLC19A2 which encodes for a high-affinity thiamine transporter disturbs the active process of thiamine uptake into the cells.[2]

Here, we report a 14-year-old male child with megaloblastic anaemia and diabetes mellitus. Sensorineural hearing loss was eventually recognised in the course of the hospital stay. Pharmacological treatment with thiamine resulted in dramatic normalisation of haemoglobin levels along with improvement of glycaemic control. This case report sensitises that early diagnosis and intervention with thiamine is required for patients presenting with anaemia, diabetes and deafness.

CASE REPORT

We hereby report a case of a 14-year-old male child, born out of non-consanguineous marriage, who is a known case of diabetes mellitus, presenting to the Paediatric Department at Cheluvamba Hospital, MMCRI, with the chief complaints of – progressive pallor, lethargy, tingling and numbness of limbs over the past 4 months.

He was on a basal-bolus regimen of injection actrapid and glargine with the insulin requirement being 2.1 IU/kg/day.

At presentation – vitals were stable. Head to toe examination was significant for severe pallor. Systemic examination was within normal limits.

Laboratory investigations revealed severe anaemia (Hb – 5.9 g%); peripheral smear showed features suggestive of megaloblastic anaemia. Corrected retic count was 3%. Periphersl smear for malarial parasite was negative. GRBS and HbA1c were 318mg/dl and 9.4% respectively. Cold agglutinin test was positive. Direct coombs test, ANA and anti TPO antibody tests were negative.

The liver function test and thyroid function test are within normal limits.

Serum Vitamin B12 was 129 pg/dl (Normal 160-950 pg/ml). Serum folic acid was 16.9 ng/ml (Normal 2.7-17 ng/ml)

Suspicion of TRMA syndrome prompted us to do a hearing evaluation of this patient. Audiometry test revealed mild sensorineural hearing loss, thereby completing the triad of TRMA syndrome.

The patient was initially managed with a blood transfusion to correct severe anaemia. Haemoglobin levels increased soon after transfusion, only to drop again after 7 days. By then, Rogers syndrome was suspected clinically. Pharmacological treatment with thiamine supplementation (100 mg per day) was initiated. Remission of anaemia along with further decreased insulin requirement was found in the subsequent follow-up visits of the patient. No improvement in the hearing loss was documented.

DISCUSSION

TRMA – it is responsive, rare, recessive, it is Rogers!

Thiamine is a water-soluble vitamin which is used for tissue growth and development. TRMA is caused by the mutation of a gene SLC19A2 which encodes for a thiamine transporter protein. Thiamine-responsive megaloblastic anaemia syndrome (TRMA) should be suspected in individuals who present with the following clinical features, which make up the triad as mentioned below:[3]

1. Megaloblastic anaemia
    a. Bone marrow examination reveals megaloblastic changes with ringed sideroblast seen often
    b. Vitamin B_{12}/folic acid levels are normal
    c. The anaemia is corrected with pharmacologic doses of thiamine (50–100 mg/day). However, it is found that anaemia can recur when thiamine is withdrawn.
2. Progressive sensorineural deafness: It is generally irreversible. Pharmacological correction with thiamine may not prevent the progression of hearing loss.
3. Diabetes mellitus: Thiamine replacement has been occasionally found to cause its remission.

The diagnosis of TRMA is made in a proband with megaloblastic anaemia with normal Vitamin B_{12}/folic acid levels, with or without diabetes mellitus or hearing loss in whom there is a response to pharmacological therapy to oral thiamine and/or identification of biallelic pathogenic variants in *SLC19A2* by molecular genetic testing.[4] Molecular genetic testing methods can include either single-gene testing or the use of a multigene panel.

In a child who presents with diabetes, refractory anaemia and hearing loss, TRMA should be considered as a possibility. Response to thiamine distinguishes TRMA from other syndromes such as Wolfram syndrome and Pearson syndrome. Although rare, prompt recognition of this syndrome at the earliest can induce remission or delay the development of diabetes and improve the quality of life in the patient.

CONCLUSION

Suspicion of TRMA must be made in a child completing the triad of the disease as mentioned earlier. Prompt recognition of the disease helps in early intervention and thus improves the quality of the patient.

Declaration of patient consent

Permission was obtained from the patient and the parents to publish the case report. Every attempt is made to ensure the anonymity of the patient.

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Case Report

Autoimmune thyroiditis in adolescents: Two different presentations

Pratibha Manjunath Patagar[1], Sudha Rudrappa[1]

[1]Department of Paediatrics, Mysore Medical College and Research Centre, Mysuru, Karnataka, India.

***Corresponding author:**
Pratibha Manjunath Patagar, Department of Paediatrics, Mysore Medical College and Research Centre, Mysuru, Karnataka, India.

pratibhapatagar@gmail.com

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ABSTRACT

Autoimmune thyroiditis is one of the most common causes of acquired hypothyroidism in children and adolescents. Both genetic susceptibility and environmental factors play a role in etiopathogenesis. We report two cases of autoimmune thyroiditis here with varied presentation. Both of them had different clinical features of hypothyroidism at presentation. On investigation, both of them had elevated thyroid-stimulating hormone (TSH), low T4 and elevated anti-Thyroid peroxidase (TPO) antibodies. Case 1 also had elevated anti-TG antibody level. Based on these findings, diagnosis of autoimmune thyroiditis was made and started on levothyroxine tablet, for which both of them showed both clinical and biochemical improvements.

Keywords: Autoimmune thyroiditis, TSH, T4, Anti-TPO and anti-TG antibody, Levothyroxine

INTRODUCTION

Autoimmune thyroiditis, also known as chronic lymphocytic thyroiditis or Hashimoto's thyroiditis, is the most common aetiology of thyroid disease in children and adolescents.[1-3] Both goitrous (Hashimoto's thyroiditis [HT]) and a non-goitrous (atrophic thyroiditis/primary myxoedema) variant of autoimmune thyroiditis have been distinguished.[2] The prevalence of autoimmune thyroiditis in childhood is an estimated 1–2% with female predominance with male-to-female ratio of 4:1–8:1 depending on the geographical region.[1,3-5] The aetiology of autoimmune thyroiditis is complex and multifactorial. The development of autoimmune thyroiditis depends on an immune defect in an individual with genetic susceptibility (80%) in conjunction with environmental factors (20%).[2,3] Approximately 50% of cases have a family history of autoimmune thyroid disease.[1] Several syndromes are associated with an increased risk for developing autoimmune hypothyroidism, including Down syndrome and Turner syndrome.[1,6] Thyroiditis is defined as evidence of 'intrathyroidal lymphocytic infiltration' with or without follicular damage.[5] The natural history is not completely known in paediatric population, it is variable, with remission, recurrence as well as the evolution to permanent hypothyroidism.[3,4] Euthyroidism is the most common initial pattern (about 52% of patients), followed by overt hypothyroidism (22.2%), subclinical hypothyroidism (19.2%) and hyperthyroidism (6.5%).[6]

CASE REPORTS

Case 1

A 14-year-old female, 1st born child to non-consanguineously married couple, was admitted with a history suggestive of urinary tract infection (UTI) later on probing mother gave

history of recent gain of weight since the past 6 months associated with poor scholastic performance and not interested in other household works. There was a history of not attaining menarche. However, she did not have a family history of delayed puberty or thyroid disorders. She had uneventful antenatal, birth history and normal psychomotor development. She was going to 9th standard with average scholastic performance previously. Now, her IQ is 78. They were taking iodised salt and there was no excessive use of cabbage or cauliflower at home. Provisional diagnosis of acquired hypothyroidism with superadded UTI was made.

On examination, her HR – 64/min, BP – 112/70 mmHg and other vitals were within normal limits.

Her weight was 42 kg (25th-50th percentile) height was 141.5 cm (3rd-10th centile) with BMI of 21.13 (between 50th and overweight) which accounts to CA=WA>HA [Table 1].

On physical examination, she had pallor, dull looking face and dry skin. Sensory motor rythm (SMR) stage was 2 which implies delayed puberty. Systemic examination was normal. There was no enlargement of the thyroid gland.

Investigation was done accordingly which showed T4-0.64 and TSH-160 suggestive hypothyroidism [Table 2]. There was deranged lipid profile, her blood sugar and BP were within normal limits [Table 3]. Ultrasonography (USG) neck was normal. Because of late age of onset, autoimmune thyroiditis was suspected and workup done which showed elevated both anti-TPO (>1000 IU/ml) and TG antibodies (>500 IU/ml) [Table 4]. Radionuclide thyroid scan and uptake study were normal. USG pelvis showed a normal size uterus (6 × 1.5 × 2.6 cm) and ovary. Diagnosis of autoimmune thyroiditis was made. The child was started on levothyroxine 2 mcg/kg/day. Urine culture showed growth of *Escherichia coli* accordingly treated with IV antibiotics. Lifestyle modifications, exercise and diet advice were given. The child showed improvement. Now, she is doing well and on follow-up.

Table 1: Anthropometric parameters of Case 1.

Parameters	Observed	Inference
Weight	42 kg	25th–50th percentile
Height	141.5 cm	3rd–10th percentile
BMI	21.13	Between 50th and overweight
Waist circumference	72 cm	Between 50th and 75th percentile
Equation	CA=WA>HA	Endocrine cause

Table 2: Thyroid function test result of Cases 1 and 2.

TFT	Case 1	Case 2	Ref. range
T3	4.8	11.6	81–178 ng/dl
T4	0.64	1.93	4.5–12.5 mcg/dl
TSH	160.0	100.0	0.4–4.2 micro IU/mL

Case 2

A 10-year, 2-month-old male, 3rd born child to non-consanguineous married couple, admitted with the complaints of not gaining height as compared to his siblings and peer group noted for 2 years. Since the past 3 months, the child was lethargic with decreased activity, had lost interest in reading and writing associated with loss of appetite but he was gaining weight. There was also a history of generalised swelling of body, constipation and cold intolerance since the past 2 months. He did not have a family history of similar complaints. The child had normal psychomotor development before this, was going to the 5th standard with average scholastic performance. Now, his IQ is 75. They were taking iodised salt and there was no excessive use of cabbage or cauliflower at home. Based on the above history, provisional diagnosis of pathological short stature secondary to hypothyroidism was made.

On examination, HR – 70/min, BP – 104/68 mmHg and other vitals were within normal limits. His weight was 30 kg (25th-50th percentile) and height was 120cm (<3rd percentile) with body mass index (BMI) of 20.83 (obese) which accounts to CA>WA>HA. Child had Midparental Height (MPH) OF 157.75+8 cm, projected height of 153 cm and Waist to hip ratio of 0.97 (obese). Waist-to-hip ratio was 0.97 (obese) [Table 5].

He had pallor, coarse face with depressed nasal bridge, dry and cold skin and non-pitting oedema (myxoedema). SMR stage was 2 which was appropriate for age. Systemic examination was normal. There was no enlargement of the gland.

Investigation was done accordingly which showed T4-1.93 and TSH-100 suggestive hypothyroidism [Table 2]. There was

Table 3: Lipid profile, haemoglobin and blood sugar levels of Cases 1 and 2.

Lipid profile	Case 1	Case 2	Ref. range
Total cholesterol	319.5	300	<200 mg/dl
Triglyceride	397.9	346	<150 mg/dl
HDL	16.9	15.8	>60 mg/dl
VLDL	79.5	95.9	<30 mg/dl
LDL	223.02	218.5	<130 mg/dl
Haemoglobin	9.9 g % (>12)	10 g % (>11.5)	
Fasting blood glucose	86 mg/dl	98 mg/dl	

Table 4: Thyroid autoantibody levels of Cases 1 and 2.

Antibody level	Case 1	Case 2	Ref. range
Anti-TPO antibody	>1000 IU/ml	500 IU/ml	<50.00 IU/ml
Anti-TG antibody	>500 IU/ml	100 IU/ml	<60.00 IU/ml

Table 5: Anthropometric parameters of Case 2.

	Observed	Inference
Weight	30 kg	25th–50th percentile
Height	120 cm	Less than 3rd percentile
BMI	20.83	Obese
Equation	CA>WA>HA	Endocrine cause
Waist circumference	62 cm	50th–75th percentile
Waist-to-hip ratio	0.97	Obese

deranged lipid profile, his blood sugar and BP were within normal limits [Table 3]. USG neck was normal. Because of late age of onset, autoimmune thyroiditis was suspected and workup done which showed elevated anti-TPO (>500 IU/ml), however, anti-TG antibodies were within normal limits [Table 4]. Diagnosis of autoimmune thyroiditis was made. The child was started on levothyroxine 2 mcg/kg/day. Lifestyle modifications, exercise and diet advice were given. The child showed improvement. Now, he is doing well and on follow-up.

DISCUSSION

Autoimmune thyroid diseases constitute both HT and Graves' disease. Both are characterised by infiltration of the thyroid by T and B lymphocytes that react against thyroid antigens and thereby producing thyroid autoantibodies. The autoantibodies are directed against thyroid peroxidase (anti-TPO), thyroglobulin (anti-TG) and thyroid-stimulating hormone receptors (TRABs).[4] Two types of autoimmune thyroiditis are causes of persistent hypothyroidism: Hashimoto's disease (goitrous form) and atrophic thyroiditis (non-goitrous form).[5]

Several studies have shown that autoimmune thyroid disease has definite genetic propensity for thyroid autoimmunity and they run in families.[7] Direct cytotoxicity by CD8 T cells is believed to be the main mechanism of hypothyroidism *in vivo*.[5] The autoimmune injury of the gland is responsible for clinical and biochemical alterations. The natural history of the disease is as follows: (1) Toxic, transient and self-limited thyroiditis; (2) euthyroid goitre and (3) hypothyroidism with/without goitre.[4] There is no fixed duration for each stage. Conversion of Hashimoto's thyroiditis into Grave's disease has been observed in at least 3–4% of children and adolescents.[8,9]

The high incidence of autoimmune thyroid diseases in females suggests the participation of X chromosome genes or even an influence by the absence of chromosome Y.[3,4,10] There is also increased risk for other autoimmune diseases, most commonly diabetes, alopecia, vitiligo and celiac disease.[11-13] In the present case, one was female and the other one was male, the patient did not meet criteria for other associated autoimmune comorbidities.

The most common symptoms of hypothyroidism include easy fatiguability, constipation, cold intolerance and menstrual irregularities. Oligomenorrhoea and/or menometrorrhagia are frequent, due to a poor conversion of oestrogen precursors.[7,14] Children may present with pubertal delay or precocious puberty.[7,13] Other features include dry, cold, yellow and thickened skin, secondary to the accumulation of hydrophilic mucoproteins in the dermis (such as hyaluronic acid) as well as the atrophy of the sweat glands. There will also be a history of obesity and short stature.[5,15,16] The most common physical examination finding is a goitre. Other findings include bradycardia, delayed reflexes and oedema of the face and extremities (myxoedema). Hypothyroidism causes poor linear growth and/or growth failure and, if undiagnosed, may compromise adult height.[3,5] In the present case, it was observed that the clinical manifestations presented by the patient correspond to the most frequently reported in the literature.

The diagnosis of autoimmune thyroiditis is established by clinical characteristics, elevated TSH, detection of serum antibodies against thyroid antigens (mainly thyroid peroxidase and thyroglobulin) as well as the presence of goitre. The serum TSH concentration is elevated in primary hypothyroidism and its determination is an appropriate screening test for thyroid dysfunction.[5] The presence of goitre on examination or elevated TSH levels should prompt the measurement of anti-TPO antibodies. Anti-thyroperoxidase (anti-TPO) antibodies are the most sensitive and best screening test in the diagnosis of autoimmune thyroiditis.[2,5] They are found in approximately 90% of the patients.[5] Antithyroid peroxidase antibody titres correlate well with the number of autoreactive lymphocytes that infiltrate the thyroid.[8] Antibodies to thyroglobulin (anti-TG), the most abundant protein in the thyroid gland, are less sensitive (positive in only 60–80% of patients) and less specific (positive in a greater proportion of healthy controls) than antithyroid peroxidase antibodies.[17] The typical patient with hypothyroidism secondary to autoimmune thyroiditis will have an elevated TSH (>10IU/mL), a low FT4 and positive anti-TPO antibodies.[5]

In the present case, both the cases had elevated TSH, low T4 and elevated anti-TPO antibodies, however, only Case 1 had elevated anti-TG antibodies while the Case 2 had normal anti-TG antibodies.

Thyroid ultrasound is an important laboratory test for the diagnosis and follow-up of cases of autoimmune thyroiditis. An irregular texture in the parenchyma in the scan is suggestive of thyroiditis. The presence of nodules or cysts requires special attention to rule out the possibility of carcinoma.[4] In adults, USG thyroid has been shown to have definite value in the diagnosis of autoimmune thyroiditis. However, the role of USG in the evaluation of autoimmune thyroiditis in paediatric population is not yet

Table 6: Levothyroxine dosing according to age.

Age in years	Levothyroxine dose (mcg/kg/day)
1–3	4–6
3–10	3–5
10–16	2–4
17 and above	1.6

defined.[18] Imaging studies (thyroid ultrasonography and/or thyroid uptake and scan) may be performed if thyroid Ab tests are negative or if a nodule is palpable, but are rarely necessary.[19] Improvements in the measurement of circulating autoantibodies and ultrasonography have obviated the need for biopsy or FNAC in the diagnosis of autoimmune thyroiditis. Both of our cases had normal ultrasound neck findings.

The treatment of acquired hypothyroidism is similar to that of congenital hypothyroidism. Levothyroxine tablets are the treatment of choice administered once daily, 15–30 min before food consumption, avoiding coadministration with calcium, iron, soy products, sucralfate, potassium-binding resins, antacids containing aluminium and bile acids binding resins.[5] Levothyroxine dosing is based on body surface area (100 μg/m^2/d) or on age and weight following the general pattern, as shown in [Table 6].[4,20]

TSH normalisation is the goal of replacement. In our practice, we aim to reach values in the lower part of the normal range (0.5–2 micro IU/mL), FT4 in the upper half of the normal range.[5] Thyroid function tests should be obtained about 6–8 weeks after the initiation or every 6–8 weeks following a change in levothyroxine dose. Once biochemical euthyroidism has been achieved, TSH can be monitored every 4–6 months, up to the attainment of final height.[5] The goals of treatment are to achieve clinical and biochemical euthyroidism and to attain normal linear growth and development throughout childhood and adolescence.[2]

Accordingly, both the cases have been started with levothyroxine tablets 2 mcg/kg/day. Thyroid function tests done after 6 weeks showed improvement.

CONCLUSION

The patient showed improvement in clinical symptoms after the replacement of levothyroxine, along with significant decrease in serum levels of TSH. As thyroid ultrasound was normal showing no calcification or increased vascularity or any nodule, there was no need for biopsy or fine needle aspiration cytology (FNAC) in this case, but follow-up should be continued to carry out further evaluations. These two case scenarios help us to know the clinical presentation of autoimmune thyroiditis in the paediatric population and hence being the most common thyroid disease in this age group.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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Journal Review

Journal watch

Vikram Sakaleshpur Kumar[1]

[1]Department of Paediatrics, Subbaiah Medical College, Shivamogga, Karnataka, India.

***Corresponding author:**
Vikram Sakaleshpur Kumar,
Department of Paediatrics,
Subbaiah Medical College,
Shivamogga, Karnataka, India.

vikramskumar@yahoo.co.in

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Source: Akunne OO, Mugabo P, Argent AC. Pharmacokinetics of vancomycin in critically ill children: A systematic review. *Eur J Drug Metab Pharmacokinet*. 2022 Jan;47(1):31-48. doi: 10.1007/s13318-021-00730-z. Epub 2021 Nov 8. PMID: 34750740; PMCID: PMC8574943.

Vancomycin is often used in the ICU for the treatment of Gram-positive bacterial infection. In critically ill children, there are pathophysiologic changes that affect the pharmacokinetics of vancomycin. This is a systematic review of vancomycin pharmacokinetics and pharmacodynamics in critically ill children.

Thirteen studies were included in this systematic review. A wide variety of dosing and sampling strategies were used in the studies. Methods for estimating vancomycin pharmacokinetics, especially the area under the curve over 24 h, varied widely between the studies. Vancomycin doses of 20–60 mg/kg were given daily. This resulted in high variability in pharmacokinetic parameters. *Vancomycin trough level was less than 15 μg/mL in most of the studies.* Vancomycin clearance ranged from 0.05 to 0.38 L/h/kg. The volume of distribution ranged from 0.1 to 1.16 L/kg. Half-life was between 2.4 and 23.6 h. Patients in the study receiving continuous vancomycin infusion had AUC_{24} <400 μg·h/mL.

This systematic review shows that there is a large variability in the pharmacokinetics of vancomycin among critically ill paediatric patients. Studies to assess the factors responsible for this variability in vancomycin pharmacokinetics are needed.

Source: De Sutter AI, Eriksson L, van Driel ML. Oral antihistamine-decongestant-analgesic combinations for the common cold. *Cochrane Database Syst Rev. 2022* Jan 21;1(1): CD004976. doi: 10.1002/14651858.CD004976.pub4. PMID: 35060618; PMCID: PMC8780136.

Although combination formulas containing antihistamines, decongestants and/or analgesics are sold over-the-counter in large quantities for the common cold, the evidence for their effectiveness is limited, yet they are being used unscrupulously. This is a Cochrane review update of a review first published in 2012. Randomised controlled trials (30 studies [6304 participants] including 31 treatment comparisons) investigating the effectiveness of antihistamine-decongestant-analgesic combinations compared with placebo, other active treatment (excluding antibiotics) or no treatment in children and adults with the common cold were selected.

The authors found a lack of data on the effectiveness of antihistamine-analgesic-decongestant combinations for the common cold. Based on these scarce data, the effect on individual symptoms is probably too small to be clinically relevant. *There is no evidence of effectiveness in young children.* In 2005, the US Food and Drug Administration issued a warning about adverse effects associated with the use of over-the-counter nasal preparations containing phenylpropanolamine.

Source: Sevinc N, Bilici N, Sevinc E, Dogan E. Blood and faecal lead levels in children with various functional gastrointestinal disorders. *An Pediatr (Engl Ed). 2022* Jan;96(1):35-42. doi: 10.1016/j.anpede.2021.02.001. Epub 2021 Mar 4. PMID: 35058019.

The researchers investigate the blood lead levels (BLLs) and faecal lead levels (FLLs) in children with various functional gastrointestinal disorders (FGIDs) such as functional constipation (FC) (n = 36), functional abdominal pain (FAP) (n = 36) and functional nausea (FN) (n = 30) and compare them with controls.

The median BLLs in the FGIDs group were significantly higher than in controls (5.12 and 1.77 μg/dL, respectively). The BLLs were above 5 μg/dL in 51.9% of children with FGIDs. There was a statistically significant difference in BLLs between FC subgroup and the other subgroups (FAP and FN) (P = 0.003 and P < 0.001, respectively). The FLLs in the FGIDs group were significantly higher than in controls (28.08 and 0.01 μg/g, respectively). There was no significant difference in FLLs between FC subgroup and the other subgroups (P = 0.992 and P = 0.989, respectively). No significant relation was found between BLLs and FLLs of the FGIDs group (P = 0.123).

This interesting and thought-provoking study revealed that *children with FGIDs had higher BLLs and FLLs than controls and also more than half of the children with FGIDs had BLLs ≥5 μg/dL which is considered a toxic level.* These results might revive the question of whether or not clinicians need to evaluate routine BLLs in children with FGIDs.

Source: Burns JC, Roberts SC, Tremoulet AH, *et al*. Infliximab versus second intravenous immunoglobulin for the treatment of resistant Kawasaki disease in the USA (KID CARE): A randomised, multicentre comparative effectiveness trial. *Lancet Child Adolesc Health. 2021*;5(12):852-861; doi: https://doi.org/10.1016/S2352-4642(21)00270-4.

Although intravenous immunoglobulin (IVIG) is an effective therapy for Kawasaki disease, 10–20% of patients have recrudescent fever as a sign of persistent inflammation and require additional treatment. The researchers aimed to compare infliximab with a second infusion of IVIG for the treatment of resistant Kawasaki disease.

Patients were randomly assigned (1:1) to a second IVIG (2 g/kg over 8–12 h) or intravenous infliximab (10 mg/kg over 2 h without premedication), using a randomly permuted block randomisation design with a block size of two or four. Patients with fever 24 h–7 days following completion of the first study treatment crossed over to receive the other study treatment. The primary outcome measure was a resolution of fever at 24 h after initiation of study treatment with no recurrence of fever attributed to Kawasaki disease within 7 days post-discharge. The secondary outcome measures included duration of fever from enrolment, duration of hospitalisation after randomisation and changes in markers of inflammation and coronary artery Z score.

There was no difference between treatment groups for markers of inflammation or coronary artery outcome. Twenty-four (44%) of 54 patients in the infliximab group and 33 (67%) of 49 in the second IVIG group had at least one adverse event. A drop in haemoglobin concentration of at least 2 g/dL was seen in 19 (33%) of 58 patients who received IVIG as either their first or second study treatment (three of whom required transfusion) and in 3 (7%) of 43 who received only infliximab (none required transfusion; P = 0.0028). Haemolytic anaemia was the only serious adverse event deemed definitely or probably related to study treatment and was reported in 9 (15%) of 58 patients who received IVIG as either their first or second study treatment and none who received infliximab only.

They conclude *that infliximab is a safe, well-tolerated and effective treatment for patients with IVIG-resistant Kawasaki disease, and results in a shorter duration of fever, reduced need for additional therapy, less severe anaemia and shorter hospitalisation compared with a second IVIG infusion.*

Source: Letouzey M, Lorthe E, Marchand-Martin L, Kayem G, Charlier C, Butin M, Mitha A, Kaminski M, Benhammou V, Ancel PY, Boileau P, Foix-L'Hélias L; EPIPAGE-2 infectious diseases working group. Early antibiotic exposure and adverse outcomes in very preterm infants at low risk of early-onset sepsis: The EPIPAGE-2 cohort study. *J Pediatr. 2022* Apr;243:91-98.e4. doi: 10.1016/j.jpeds.2021.11.075. Epub 2021 Dec 21. PMID: 34942178.

The researchers set out to assess the association between early empirical antibiotics and neonatal adverse outcomes in very preterm infants without risk factors for early-onset sepsis (EOS). This is a secondary analysis of the EPIPAGE-2 study, a prospective national population-based cohort that included all live-born infants at 22–31 completed weeks of gestation in France in 2011. Infants at high risk of EOS (i.e., born after preterm labour or preterm premature rupture of membranes or from a mother who had clinical chorioamnionitis or had received antibiotics during the past 72 h) were excluded from the study. Early antibiotic exposure was defined as antibiotic therapy starting at day 0 or day 1 of life, irrespective of the duration and type of antibiotics.

Among 648 very preterm infants at low risk of EOS, 173 (26.2%) had received early antibiotic treatment. Early antibiotic exposure was not associated with death or late-

onset sepsis or necrotising enterocolitis; however, it was associated with higher odds of severe cerebral lesions and moderate-severe bronchopulmonary dysplasia (BPD). *Early empirical antibiotic therapy administrated in very preterm infants at low risk of EOS was associated with a higher risk of severe cerebral lesions and moderate-severe BPD.*

Source: Storm DW, Copp HL, Halverson TM, Du J, Juhr D, Wolfe AJ. A child's urine is not sterile: A pilot study evaluating the paediatric urinary microbiome. *J Pediatr Urol. 2022* Mar 4:S1477-5131(22)00092-4. doi: 10.1016/j.jpurol.2022.02.025. Epub ahead of print. PMID: 35337731.

A bladder microbiome (urobiome) exists in adults. Data support the effects of the adult urobiome on urinary tract health with associations between dysbiotic urobiomes and lower urinary tract disorders. Understanding urobiome origin is important since other microbiomes establish around birth and microbiome alterations are linked to disease development. However, the paediatric urobiome has not been well studied.

Seventy-four children <18 years of age without recent antibiotic exposure were recruited, including 48 males and 26 females, aged 2 weeks–to 209 months of age. Transurethral catheterised urine samples and samples from the perineum, urethra, vagina and foreskin were collected. Specimens were assessed using the expanded quantitative urine culture protocol and by 16S rRNA gene sequencing. Dada2 was used to profile microbial compositions, and BLCA was used to identify microbial taxa. Bacteria were detected in 90.5% of urine samples and identified in children as young as 2 weeks of age. Microbial communities and compositions of the female bladder and other urogenital niches (urethra, perineum and vagina) differed significantly by age. Lactobacillus predominated the bladder, urethral and vaginal microbiomes in post-pubertal girls. Compared to female urinary microbiomes, those of males differed less substantially. Only perineal microbiomes differed significantly by age, whereas male urethral and foreskin microbiomes did not differ significantly.

A paediatric urobiome exists, with differences between males and females and can be detected at a young age with changes occurring throughout childhood. Similarities and differences are also seen between the paediatric urobiome and adjacent niches.

Source: Neena R, Remya S, Anantharaman G. Acute acquired comitant esotropia precipitated by excessive near work during the COVID-19-induced home confinement. *Indian J Ophthalmol. 2022* Apr;70(4):1359-1364. doi: 10.4103/ijo.IJO_2813_21. PMID: 35326055.

The authors conduct a retrospective, clinical study to evaluate the causes of acute acquired comitant esotropia (AACE) in young adults and children in the setting of COVID-19-induced home confinement, who presented to the Paediatric Ophthalmology and Strabismus services of a tertiary eye care centre in South India from August 2020 to January 2021 during the COVID-19 pandemic.

Eleven (73.3%) of the total 15 patients were students, above 10 years and with a mean age of 16.8 years. Twelve patients (80%) had more than 8 h of near activity a day with a mean duration of 8.6 h/day. The most common near activity was online classes, followed by job-related work and mobile games, and 86.7% used smartphones for near work. The average esotropia was 22.73 prism Diopter (PD) for distance and 18.73 PD for near. A majority (66.6%) had hyperopia with basic or divergence insufficiency esotropia, and the remaining 33.3% had myopia and fitted into the Bielschowsky type AACE. There was no precipitating event other than sustained near work in all, except in one patient who also had a fever before the onset of esotropia.

The authors conclude that *the habit of a long time and sustained near work, especially on smartphones, may increase the risk of inducement of AACE.*

Source: Keene JC, Morgan LA, Abend NS, Bates SV, Bauer Huang SL, Chang T, Chu CJ, Glass HC, Massey SL, Ostrander B, Pardo AC, Press CA, Soul JS, Shellhaas RA, Thomas C, Natarajan N. Treatment of neonatal seizures: Comparison of treatment pathways from 11 neonatal intensive care units. *Pediatr Neurol. 2022* Mar;128:67-74. doi: 10.1016/j.pediatrneurol.2021.10.004. Epub 2021 Oct 11. PMID: 34750046.

The authors conducted a descriptive analysis of 11 neonatal seizure management pathways from Level IV neonatal intensive care units in the United States that specialise in neonatal neurocritical care including guidelines for electroencephalography (EEG) monitoring, antiseizure medication (ASM) choice, timing and dose to highlight areas of consensus and describe aspects of variability.

All sites had 24/7 conventional EEG initiation, monitoring and review capability. Management pathways uniformly included prompt EEG confirmation of seizures. Most pathways included a provision for intravenous benzodiazepine administration if either EEG or loading of ASM was delayed. Phenobarbital 20 mg/kg IV was the first-line ASM in all pathways. Pathways included either fosphenytoin or levetiracetam as the second-line ASM with variable dosing. The third-line ASMs were most commonly fosphenytoin or levetiracetam, with alternatives including topiramate or lacosamide. All pathways provided escalation to continuous midazolam infusion with variable dosing for seizures refractory to initial medication trials. Three pathways also included lidocaine infusion. Nine pathways discussed ASM discontinuation after resolution of acute symptomatic seizures with variable timing.

The authors conclude that, despite a paucity of data from controlled trials regarding optimal neonatal seizure management, *there are areas of broad agreement among institutional pathways. However, there are also areas of substantial heterogeneity that requires further research and includes optimal second-line ASM, dosage and timing of ASM discontinuation.*

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

Dr. Vikram Sakaleshpur Kumar is in the Editorial Board of the journal.

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