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Karnataka Pediatric Journal

Editorial

From the desk of editor-in-chief

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Respected members of IAP Karnataka,

Greetings from Karnataka Pediatric Journal!

With immense pleasure, I am presenting the second issue of the flagship journal of IAP Karnataka. I am happy to receive the positive feedback for the journal from our mentors and members. The editorial board will strive to continue and maintain the standard of the journal. With the support from our esteemed members, I am sure the journal will get indexed soon.

The present issue has very interesting articles. In the review articles on skin prick testing and food allergy, the authors have described the mechanisms, diagnosis, and management of these allergies in children. Pediatricians are increasingly be encountering various allergic conditions such as atopic dermatitis, food allergies, allergic rhinitis, and asthma in their day-to-day practice. Accurate diagnosis of allergies depends very much on a detailed history supported by the judicious use of allergy tests. The history should focus first on confirming the diagnosis of allergy and then identifying the potential allergen. Investigations should be guided by the history and performed judiciously.

As the focus has been shifted to the prevention of infections in keeping the environment more sterile and minimalist interaction between human, animals, and microbiota, it has seen the surge of allergic diseases in the past 3 decades. There has been an increased emergence of food allergies in the past two decades with awareness of common foods causing food allergy. At present, the research focus is on treatment and any measures which can help in prevention of food allergies. Early use of broad-spectrum antibiotics in the 1st year of life and cesarean section will disturb normal healthy microbiota development in gut resulting in dysbiosis and predilection of allergies. Advice for unnecessary avoidance of foods must be given with discretion to parents, bearing in mind, that this can cause micronutrient deficiency in children, if done without proper scientific reason.

The first few hours and days of a newborn's life are a critical window for establishing lactation and providing mothers with the support they need to breastfeed successfully. Baby-friendly hospital initiative, since 1991, has helped to motivate facilities providing maternity and newborn services worldwide to better support breastfeeding. The author has described various steps of successful breastfeeding in simple language.

Renal tubular acidosis is a common inherited tubulopathy in children. Proximal renal tubular acidosis, usually secondary to a systemic metabolic disease, is characterized by a generalized dysfunction of the proximal tubule resulting in Fanconi syndrome. In addition to supportive therapy, specific treatment for the underlying etiology and regular monitoring of growth and laboratory parameters are of utmost importance.

Polycystic ovarian syndrome (PCOS) is the most common female endocrinopathy. Clinical features of PCOS are usually evident in adolescence. PCOS may clinically manifest for the 1st time in adolescence. Hyperandrogenemia and oligoanovulation are the two essential criteria for the diagnosis of PCOS. It has long-term effects on cardiovascular, endocrinal, reproductive, and metabolic health. Early management of PCOS mitigates its long-term effects on health. Therapeutic lifestyle management and psychological counseling form the main stay of treatment in adolescence. Diagnosis of PCOS in adolescence is revisited and confirmed in adulthood. Management of PCOS is multidisciplinary and requires long-term regular follow-up in adolescence and adulthood. This has been discussed by the author in detail which will definitely benefit the pediatricians in the management of such adolescents.

Monitoring of lung functions is mandatory for diagnosis and further management of asthmatic patients. Spirometry, the widely available investigation, is the gold standard test used for mapping pulmonary dynamicity. It has got its own limitations in the form of operational difficulties in children, the elderly, and in those with neuromuscular or behavioral issues. In the current era of COVID-19 pandemic, the utility of spirometry has been further restricted to selected cohort only, due to potential risk of viral transmission during the procedure. There are certain distinct advantages of oscillometry over spirometry. People with neuromuscular weakness, cognitive limitations, and the elderly can easily perform it with only minor understanding and effort. Oscillometry is more sensitive than spirometry in detecting peripheral airway diseases. Less aerosol generation during the normal tidal breath is another advantage of oscillometry, over spirometry needing forceful efforts, which makes it more suitable for use in viral pandemic situations for monitoring patients with both asthma and pneumonia.

Although much is spoken about breaking bad news by medical professionals, there is very little information on parents' perspective of this experience. Study of the parents' satisfaction with the experience of receiving the diagnosis of Down syndrome (DS) for their child has been evaluated in this original article. Children studying in special schools with DS were identified and a retrospective study of their parents' experience on receiving their child's diagnosis was done using a semi-structured questionnaire. Factors associated with satisfaction and avoidance of factors causing dissatisfaction will help improve the perception of these parents toward the condition.

The original article on perinatal outcome of hypertensive disorders of pregnancy (HDP) assessed the incidence of HDP and its correlation with perinatal outcomes. HDP are multisystem diseases, which may complicate 5–10% of all pregnancies and are leading causes of maternal and perinatal mortality and morbidity worldwide. This study has shown useful insights into incidence of hypertensive disorders of pregnancy and perinatal outcomes in comparison to normal pregnancy.

There are three interesting case reports on congenital eyelid imbrication syndrome, subaponeurotic fluid collection, and neonatal Group B streptococcal osteomyelitis and suppurative arthritis which the readers will find it very interesting. I thank the editorial board members, authors, and reviewers for their support in bringing out this issue.

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Karnataka Pediatric Journal

Review Article

Skin prick testing in children

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ABSTRACT

There is an increasing incidence of allergies across all the ages in India. Pediatricians of the future will increasingly be encountering various allergic conditions. Accurate diagnosis of allergies depends very much on a detailed history supported by the judicious use of allergy tests. The two widely available allergic tests in our country are the skin prick testing (SPT) and serum-specific IgE. This article discusses in detail about the various aspects of SPT including the indications, technique of SPT, interpretation of the results, advantages, and limitations of SPT.

Keywords: Skin prick testing in children, Diagnosis of allergy in children, Allergy testing in children

INTRODUCTION

There is an increasing incidence of allergies across all the ages in India.[1] Pediatricians of the future will increasingly be encountering various allergic conditions such as atopic dermatitis, food allergies, allergic rhinitis, and asthma in their day-to-day practice. Accurate diagnosis of allergies depends very much on a detailed history supported by the judicious use of allergy tests. The history should focus first on confirming the diagnosis of allergy and then identifying the potential allergen.[2] Investigations should be guided by the history and performed judiciously. Blanket testing will only lead to confusion to both the patient and the doctor. Allergic reactions can be IgE mediated, non-IgE mediated, or a mixture of both. This understanding is important because the commonly used allergy tests diagnose only the IgE-mediated reactions. It is also important to differentiate between sensitization and clinical allergy. A person is said to be sensitized when he makes IgE antibodies against the allergen (demonstrated by a positive skin prick testing [SPT] or specific IgE [sIgE]). However, he may or may not have clinical allergy (demonstrated by symptoms when exposed to the allergen). This knowledge is important when interpreting the allergy tests. The two widely available allergic tests in our country are the SPT and serum sIgE. SPT is considered the gold standard for aeroallergens,[3] while double-blinded placebo-controlled food challenge remains the gold standard for food allergy.[4] However, as oral food challenge is dependent on expertise and resources, physicians use SPT and sIgE for diagnosis of food allergy as well.

BLOOD TESTS

Non-specific tests such as total IgE and absolute eosinophil count are not useful in the diagnosis of allergy as these can be elevated in many other conditions.[5] The blood investigation of choice is serum sIgE to individual allergens. The standardized method for sIgE available in India is the ImmunoCAP test[6] that uses fluorescent enzyme immunoassay technique. The advantages

of sIgE are the safety, availability, and reproducibility.[7] The disadvantages are the false positivity, cost involved, and delayed results. The false positivity is due to cross-reactivity among the epitopes of various allergens. Component resolved diagnosis where sIgE to specific allergenic epitopes is tested, hopes to overcome this problem in the future.

SKIN TESTS

The various skin tests include the epicutaneous or percutaneous test, intradermal test, and patch test. The intradermal tests are used in limited conditions such as allergy to drugs, vaccines, and insect venom. It requires high expertise and carries greater risk of adverse effects.[8] The patch test is used for testing delayed hypersensitivity reactions like contact dermatitis. The percutaneous skin test is widely practiced as it is easy to perform, has low risk of side effects, and gives good results when performed and interpreted accurately. It can be done by scratch, puncture, and prick techniques. Of the three techniques, percutaneous SPT is the most popular and commonly used test. This article discusses further about the SPT.

INDICATIONS FOR SPT

SPT is indicated where IgE-mediated allergic mechanism is suspected such as atopic dermatitis, allergic rhinoconjunctivitis, asthma, food allergy, drug allergy, latex allergy, urticaria, and anaphylaxis.[9] Other less common conditions include allergic bronchopulmonary aspergillosis, eosinophilic esophagitis, and gastroenteritis.

The common inhaled allergens (aeroallergens) across the world are house dust mites, pollen, animal dander, molds, and cockroaches. The common food allergens across the world are cow's milk, hen's egg, soy, wheat, pea nuts, tree nuts, fish, and sea food. In addition, pediatricians should also have an understanding of the locally prevalent allergens which can vary from place to place.[10,11]

MECHANISM OF SPT

SPT uses cutaneous sensitivity as a surrogate marker for sensitization in target organs such as skin, eyes, nose, lungs, and gut.[9] Whenever an allergic person is exposed to an allergen, his immune system makes IgE antibodies. These antibodies remain attached to the surface of mast cells. During SPT, when the allergen is introduced into the skin, it interacts with IgE bound to the cutaneous mast cells. Cross-linking of the immunoglobulins occurs leading to release of histamine and other chemical mediators. This produces a local allergic reaction in the form of wheal and flare. This local reaction is measured and compared with histamine taken as positive control and normal saline taken as negative control. As the epidermis is relatively free of blood vessels and pain fibers, when performed appropriately, the SPT should not cause major discomfort or bleeding.

CONTRAINDICATIONS FOR SPT

SPT is contraindicated where there is an extensive skin disease (e.g., atopic dermatitis) with very little normal skin, skin conditions such as urticaria and severe dermatographism, poor patient cooperation, and patient unable to stop drugs that can interfere with SPT.

It should be done cautiously in very young infants, pregnant women, severe asthma, history of anaphylaxis, conditions associated with elevated tryptase levels, and patient on drugs that can increase the risk of severe allergic reactions (beta-blockers, ACE inhibitors, etc.). SPT in these circumstances should be done at controlled settings by experienced practitioners.

PREPARATION FOR SPT

We should ensure that the patients do not use drugs that can interfere with the result of SPT for the duration of action of these drugs. Antihistamines suppress the histamine response for a variable period of time. In general, first-generation antihistamines can be stopped for 72 h. Second-generation antihistamines suppress histamine response for a variable length of time, up to 7 days.[12] Leukotriene receptor antagonists do not affect the skin reactivity.[12] Short-term oral corticosteroid treatment does not seem to alter the reactivity to SPT.[13] Topical steroids can affect reactivity of SPT[14] and some studies have shown that the inhibitory effect of short-term topical steroids lasts for 3 days.[15] However, other studies have shown that application of potent topical steroids can affect SPT reactivity for 3 weeks.[16] Topical calcineurin inhibitors have a variable affect. Pimecrolimus does not affect histamine testing[17] but tacrolimus seems to affect it.[18] However, animal studies have shown that tacrolimus has no effect on immediate reactions but decreased some late-phase reactions.[19] Therefore, no withdrawal is recommended to evaluate only immediate reactions, but a 4-week withdrawal may be necessary for the evaluation of late-phase reactions.

Patients are explained about the procedure and consent obtained. They should be reassured that the test will cause only mild discomfort. All materials needed for SPT are kept ready before the test. This includes standard allergen extracts, lancets for skin prick, marker pens, and tissues for wiping the skin after the procedure. Resources to manage any severe reactions, such as IM adrenaline, oxygen source, inhaled salbutamol, IV fluids, and resuscitation equipment, should be kept ready.[8] It is important that standard commercial reagents are chosen for the procedure as the

quality of reagents determines the outcome of the SPT. The commercially available allergen extracts in India have good practical utility though these are not standard. Where standard commercial allergen extracts are not available, a prick-to-prick technique can be done by pricking fresh food with the lancet and then pricking the skin.[8]

DEVICES USED FOR SPT

SPT requires a sharp pointed lancet that is used to prick through the allergen extract and into the superficial layers of the skin. The lancets come in different shapes and sizes and the choice depends on comfort, cost, and availability. The lancets can be dipped in allergen extracts and then pricked into the skin; or a drop of allergen extract is placed on the skin and the lancet pricked through it.

They can be single tip, double tipped (duo tip) or have multiple tips. They also come as single separate lancets for each allergen or have multiple point lancets to test multiple allergens simultaneously [Figure 1].

SPT PROCEDURE

The skin is cleaned with alcohol swab before the procedure and allowed to dry. The skin of forearm and back is usually used for this purpose. The forearm is less sensitive than the back.[20] When forearm is used, pricks are done 2–3 cm away from wrist and cubital fossa. The skin is then marked with numbers to identify the corresponding allergens. Care is taken to maintain a gap of 2 cm between two allergens to avoid false-positive reactions due to overlap.[20] A drop of allergen is placed adjacent to the corresponding number. The lancet is passed through the drop and the skin at an angle of approximately 45 degrees. The device is then lifted, creating a small break in the epidermis. It is estimated that only 0.3 μl of fluid is introduced into the skin.[21] Using the lancet, the allergen is driven into the superficial layers of the skin by means of a gentle prick. The excess solution is mopped off using a tissue paper.

Performed properly, SPT should not produce major discomfort or bleeding.[8] The number of allergens used for testing depends on the clinical condition and the suspected allergens. The same lancet should not be used for testing multiple allergens. The histamine is read 10–15 min later and allergens 15–20 min later. As histamine produces wheal early compared to the individual allergens, it can be pricked at the end after the individual allergens. The diameter of the wheal is measured horizontally and vertically and the mean diameter is recorded in mm.[22] Some people take the largest diameter of the wheal into consideration. The flare is measured in similar method and recorded separately. Sometimes, irregular extensions of the wheal (pseudopods) can be noted. Their significance is not known.[8] After 20 min, the reaction may fade away and the test might have to be repeated again if not interpreted in time.

In high-risk cases, patient is observed for 20–30 min in the clinic after completion of the test.[23] The patient is observed for any signs and symptoms of systemic allergic reactions mentioned below.

The reagents should be stored in the refrigerator at the designated temperature. Care should be taken to leave the reagent outside the refrigerator for the shortest possible time. Care should be taken to avoid bacterial contamination and cross-contamination with other allergens. They should be discarded after the expiry date.

INTERPRETATION OF SPT RESULTS

For positive control (histamine), a wheal diameter of ≥3 mm (at least 3 mm greater than negative control) is taken as positive.[8] A wheal diameter of <3 mm for positive control might be seen if the patient is taking drugs with antihistamine activity or has non-reactive skin. In this case, it is not possible to go ahead with the SPT.

A wheal >3 mm for negative control (normal saline) indicates a highly reactogenic skin (e.g., dermatographism), making SPT invalid.[24]

In case of individual allergens, a wheal diameter of ≥3 mm (at least 3 mm greater than negative control) is taken as a positive test [Figure 2]. The larger the wheal, the greater the likely hood of an allergic reaction when exposed to the allergen. However, a larger size does not necessarily correspond to more severe reaction.

False-positive reactions can occur in certain skin conditions (e.g., dermatographism), naturally occurring histamine in some allergen extracts, non-standard reagents, and cross-reactivity with allergens with homologous proteins.[8]

False-negative tests can occur in patients taking drugs with antihistamine activity, recent history of anaphylaxis (<4 weeks), non-standard reagents, improper technique, and UV light exposure.[8]

ADVANTAGES OF SPT

When performed and interpreted correctly, SPT is highly sensitive for IgE-mediated allergies.[25]

They are relatively cheap and easy to interpret. This is particularly important in a country like India.

When right technique is used, SPT is minimally invasive and should cause very little discomfort.

The results are immediately available to the family and necessary counseling can be done at the same visit. This visible reaction may act as a motivation to the family for allergen avoidance measures and appropriate treatment.

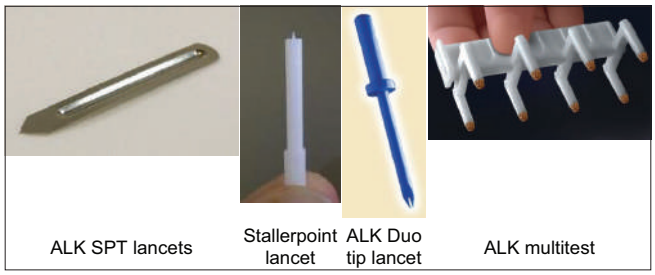

Figure 1: Picture depicting different lancets available for skin prick testing.[8]

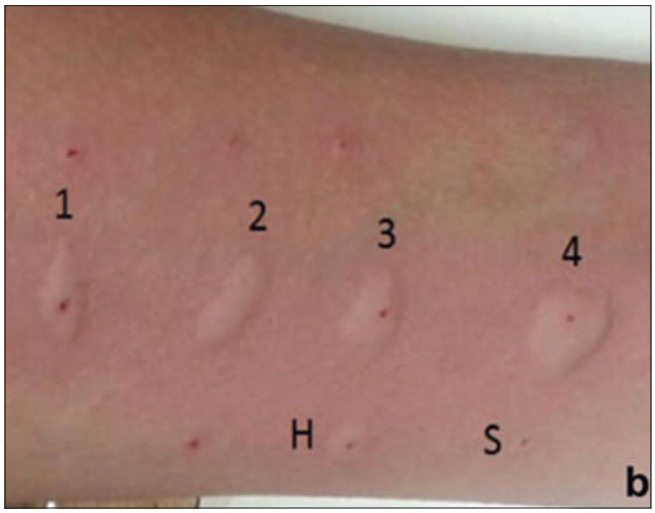

Figure 2: Picture showing wheal and flare reaction after a skin prick testing using histamine (h), saline (s), and various allergens (marked 1–4). Reproduced with permission from Gupta N, Indian pediatrics 2019.

Unlike *in vitro* tests, the results may not affected by conditions associated with high total IgE levels.[8]

Limitations of SPT

SPT results can be variable and depend on the quality of the reagent, the technique used and proper interpretation of results.[6]

The availability of standard reagents can be a challenge in our country. This can affect the quality of the test.

It needs some normal area of skin to test and cannot be done in patients where extensive area of skin is involved.

SPT cannot be done where the patient cannot stop taking drugs with antihistamine activity that can interfere with the results.

The testing requires patient cooperation and may be slightly difficult in very young infants.

Because of the possibility of systemic allergic reactions, they should be performed only in settings where severe allergic reactions can be managed.

SIDE EFFECTS OF SPT

Some patients experience mild discomfort and itching at the site of SPT. This is usually transient and self-limiting. Rarely, delayed local, painful swelling may occur due to IgE-mediated delayed reaction.

Non-allergic reactions such as infection, headache, syncope, and malaise are very rare.

Although very rare, systemic allergic reactions (including anaphylaxis) are known to occur following SPT.[26] Valyasevi *et al*. studied the incidence of systemic reactions in 497,656 skin tests and found 33 systemic reactions per 100,000 skin tests.[26] However, the reactions were mild and recovered within 1 h.

The incidence of systemic reactions was higher when testing was done for latex, antibiotics, and food allergy (especially when raw foods are used) and intradermal method of testing was used. Patient factors that were associated with increased risk of systemic reactions include young infants, pregnant women, uncontrolled asthma, previous history of anaphylaxis,[27] patients using ACE inhibitors and beta-blockers (diminished response to adrenaline treatment), and elevated baseline tryptase levels. Clinicians should exercise extra caution in the above circumstances.

CONCLUSION

SPT is a safe, reliable, and sensitive test. It is considered the gold standard for diagnosis of aeroallergens and is considered superior to sIgE. However, it is inferior to oral food challenge in diagnosis of food allergies.

It is inexpensive and the results are immediately available; definite advantages in a country like ours.

Once diagnosis of allergy is confirmed by SPT, targeted allergen avoidance measures can be advised.

An appropriate allergy management plan including recognition and management of severe allergic reactions can be given to the family. Immunotherapy can be advised where appropriate.

The performance and interpretation of the SPTs should be done by a person who is trained in diagnosis and management of allergy in children.

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 Pediatric Journal

Review Article

Breastfeeding in the first hour of birth: Science and skills

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ABSTRACT

Immediate and uninterrupted skin-to-skin contact between mother and newborn should be facilitated soon after birth to initiate breastfeeding. It initiates the newborn infant's internal process to go through nine instinctive steps (namely, crying, relaxation, awakening, activity, resting, crawling, familiarization, suckling, and sleeping). Skin-to-skin contact with the mother soon after birth contributes to an early coordination of five senses in the newborn, namely, sight, hearing, touch, taste, and smell. The oxytocin surge in the 1st h of birth makes mother to keep the infant close to her chest and also establishes chemical connection between the two. The colostrum odor increases the amount of oxygenated hemoglobin over the olfactory cortex in the newborn within 24 h of life. The skin-to-skin provides the initial colonization of the baby's microbiome outside the mother. Finally, skin-to-skin contact not only improves the bonding between mother and the infant but also influences infant's self-regulation in the years to come.

Keywords: Breastfeeding, Skin-to-skin contact, Nine instinctive sages, Catecholamine surge

INTRODUCTION

The 1st few hours and days of a newborn's life are a critical window for establishing lactation and providing mothers with the support they need to breastfeed successfully. Baby friendly hospital initiative, since 1991 has helped to motivate facilities providing maternity and newborn services worldwide to better support breastfeeding.[1]

WHO and UNICEF in April 2018 issued new ten steps guidance to increase support for breastfeeding in health facilities that provide maternity and newborn services.

The 2017 WHO guidelines, revision of the ten steps: Protecting, promoting, and supporting breastfeeding in facilities providing maternity and newborn services examined the evidence for each of the original ten steps that were originally published in 1989. Based on the new guidelines, implementation guidance rewords the ten steps while maintaining the basic theme of each step.[2]

Step 4 states, facilitate immediate and uninterrupted skin-to-skin contact and support mothers to initiate breastfeeding as soon as possible after birth with the understanding that the newborn infant will self-attach.

This write up focuses on the Importance of skin to skin in contact the 1st hour of birth in establishing breastfeeding and its associated long-term implications. The expertise of the nine instinctive stages comes from experience as well as analyses of video tapes of feeding behavior developing in newborn's in skin-to-skin contact by the research team of Widstrom *et al.*[3]

Being in skin-to-skin contact with the mother immediately after birth elicits the newborn infant's internal process to go through nine instinctive stages:

Birth cry, relaxation, awakening, activity, rest, crawling, familiarization, suckling, and sleeping.

This is applicable to normal vaginal delivery, to healthy, alert, full-term infant placed skin-to-skin with the mother during the 1st hour after birth.

Skin-to-skin contact with the mother after birth contributes to an early coordination of infants five senses: Sight, hearing, touch, taste, and smell as well as movement. Oxytocin is released in the mother's blood vessels during the 1st h after birth and contracts the uterus, facilitates placental expulsion, and decreases blood loss. This oxytocin surge increases maternal sensitivity, as shown by the mother's desire to keep her infant close after the newborn suckled or even just touched her nipple during the 1st h while skin to skin.

The mother is attracted to the infants smell, facilitating the chemical communication between the two. She should have access to the bare head of the baby, to smell. In normal vaginal delivery, there are high catecholamine's levels in newborn close to birth stimulated by the pressure of the baby's head on the birth canal.

High catecholamines are also responsible for higher pain threshold and this is nature's way to relieve pain while passing through the birth canal.

The odor of the mother's colostrums increases the amount of oxygenated hemoglobin over the olfactory cortex in the newborn infant less than 24 h old. Increased sensitivity to the odor of breast milk indicates a physiologically based early sensitive period.

This also matches the enhancements of the mother's breast odor, through the increase of the surface of the areola and Montgomery gland secretions during the corresponding time.

THE NINE INSTINCTIVE STAGES AND THEIR RELEVANCE ARE AS FOLLOWS

Stage 1 the birth cry

This cry has the effect of cleaning the airway off amniotic fluid. The extremely high catecholamine levels at birth help in absorbing liquid from the airway. When the lungs expand the transition in utero happens with oxygenation of lungs, facilitated by the birth cry. further all survival insitcts are depended on oxygenated lungs. Gently place the newborn on the mother's chest in the drainage position (tilted with the head lower than the torso and head slightly to the side) allowing the fluid to flow freely from the mouth and nose. Mother should be in a semi reclined position. Baby is length wise with the head on the mother's chest and above her breasts, ensures that pregnant women wear suitable cloths before entering delivery room to facilitate skin-to-skin contact.

Once in skin-to-skin position, cover the baby with a suitable cloth but leave the face uncovered. Skin-to-skin contact reduces the duration of third stage of labor. Cord clamping should be delayed (>180 s) after delivery and ensure that the cord length is left long and the cord clamp does not interfere with skin-to-skin contact.

Stage 2 relaxation stage

During this stage, the new born infant is still and quiet, lying quietly on the mother's chest, the baby hears the mother's heart beat to which s/he is accustomed and familiar while *in utero*.

The baby's temporarily impaired sensation at birth, due to high catecholamine's has decreased sensitivity to the surrounding. APGAR score assessment can be done on a healthy full-term newborn infant without disturbing the infant and allowing skin-to-skin to continue uninterrupted! Furthermore, injection Vitamin K should be administered during this period, as the baby's reaction to pain in this period is reduced.

Stage 3 awakening

It is a stage of transition from the relaxation stage to the activity stage. They with gradually open their eyes, blinking repeatedly until the eyes are stable and focused.

Stage 4 activity

During this stage of activity, the baby exhibits a greater range of motion throughout – the head, body, arms, and hands. The limbs move with great determination with hand-to-nipple-to-mouth movements, catch the nipple, and explore mother's chest. Rooting becomes more obvious during this stage.

During pregnancy, the nipple has become hyper pigmented and makes it easy for the newborn infant to discover the breast. Soon after birth the areola expands and takes a bulb like shape, Montgomery glands also become more pronounced. The scent of areolar secretions has been linked to head turning and directional crawling. This odor helps the infant find the nipple. The NB recognizes the scent of the mother's breast from the amniotic fluid, touches the breast, and transmits the taste of the breast to the mouth (hand-to-breast-mouth movement). This stimulates rooting and crawling movements. After the NB has located the nipple by sight, the mother's voice will attract the baby's attention to her face. The connection between the taste of the amniotic fluid and scent of the breast from the Montgomery glands highlights – a biological survival mechanism, a pathway of flavor with lifelong consequence.

During skin-to-skin contact with the mother around half an hour after birth, the NB searches for eye-to-eye contact. Infant mother bonding during pupillary contagion (respond to pupil size with changes to owns own) – first movement of eye-to-eye contact is an unforgettable experience by mother which she remembers always. These complex experiences of the newborn infant encompass more than simply a journey to the breast and the opportunity to eye contact emphasis the important of instinctive behavior during this time and avoidance of interruption.

Stage 5 resting

The resting stage is intervened with all of the other stages. A baby may stop or start during any of the stage to rest, and then continue with the same stage or move on to the next. The baby could be lying still sucking on fingers or just gazing at the nipple. The eye may be open or closed. It is crucial to allow the NB infant to take these pauses throughout the 1st h or so without being interrupted or separated. If the NB is separated and then returned, the stages will start all over again.

These resting stages are similar to "adult awake rest," which is required for consolidation of memories and contribution to learning.

Stage 6 crawling stage

It is the stage where the baby moves from the position between the breasts to a position very close to the nipple.

To prevent sliding of the baby, place towel or pillow below mother's arm, this also helps the baby to find the nipple and grasp it and prevents exhaustion, due to repeated sliding off!

The evolutionary purpose behind the NB infant's innate stepping reflex becomes clear as the NB infant crawls to the mother's breast (breast crawl). The movement of these steps of the feet over the uterus may contribute to the contraction of the uterus and decreases the time to expel the placenta and decreased blood loss. Mother can assist crawling by placing her hand under the newborn infant foot to give the baby something to push against to move toward the breast.

Stage 7 familiarization

The baby is prone on a semi reclined mother. The baby should maneuver to an appropriate position to reach the breast. The NB performs specific soliciting calls to mother –a short clinging call that results in a gentle response from the mother. The frequency increasing as s/he gets closer to the mother's nipple, odors from the breast induce this response. This phase lasts for 20 min or more. Baby familiarizes with the breast by licking the nipple and areola. This action by baby massages the breast and increases oxytocin levels and also shapes the nipple by licking. As baby smells and tastes the breast, the actions become more rigorous and more coordinated. The NB is preparing the tongue, breast, and nipple for the moment of attachment and suckling. NB infant thus practices the coordination of rooting-tongue reflex. Thus, perfecting many important oral-motor-functions, which is vital to initiate the suckling process. There is resting stage between familiarization and suckling stage. It is common for the baby to attach, once, or twice and then disengage. The NB must be allowed to do these moves to adjust into instinctive position, which is conducive to the NB infant's chin making an initial contact with the mother's breast as the baby endeavors to catch the nipple. "Chin-first contact" is associated with sustained deep rhythmical suckling.

Stage 8 suckling

It is the stage of success! The NB infant does not need help to adjust the latch. Babies who self-attach during the 1st h after birth have few problems with breastfeeding latch and milk transfer.

Skin-to-skin in the 1st h strengthens the mother's self-confidence, including decreasing the concerns about having enough milk. When babies are placed skin-to-skin with the mother, they have more optimal blood glucose levels.

Stage 9 sleeping

Toward the end of suckling, about an hour or half after birth the NB becomes drowsy and falls asleep. Oxytocin released by mother and infant suckling triggers the release of gastrointestinal hormones cholecystokinin and gastrin. These help mother and infant for a relaxing and satisfying post-prandial sleep. It also improves maternal and infant nutritional absorption.

LONG-TERM BENEFITS OF SKIN-TO-SKIN CONTACT

The microbial colonization of the infant begins before birth and continues through the birth canal. The skin-to-skin contact provides the initial colonization of the NB'S microbiome outside of the mother. Yet another reason not to bathe the baby immediately after birth (prevention of hypothermia, hospital acquired infection, etc., are other reasons).

As the hour's progresses, the first tastes of colostrum will provide vital sustenance to the infants developing gut microbiota, implicated in the expression of genes. This optimal microbiome has been implicated in long-term health including decreasing obesity and metabolic disease.

The temperature of the mother's breast increases when in skin-to-skin contact as evidenced by an increase of NB's foot temperature is an indication of the negative effect of the stress of being born.

Skin-to-skin is also linked to infant's self-regulation, a part of the concept of self-control and improved mother/infant mutuality year later.

Thus, self-control at the age of 4 years has consequences to adulthood in terms of decreased drug addiction, criminal behaviors, education, and income.

These are positive long-term consequences of skin-to-skin which also helps in parenting by protecting against parental roughness, decreased child maltreatment, and laying a foundation for the child's self-regulation and self-control.

CONCLUSION

Early initiation of breastfeeding within the first hour of life and uninterrupted skin to skin contact between mother and baby immediately after birth initiates the 9 instinctive stages of breastfeeding. this not only contributes to coordination of 5 senses and establishes a chemical connection between mother and baby but also has a long term impact on child's self regulation in Future years. such a beneficial and natural process should be promoted and practiced.

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 Pediatric Journal

Review Article

Dealing with adolescent not a child's play

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ABSTRACT

Adolescents are one-third of the country's population and dealing with adolescents is not a child's play. According to the WHO, around 1.2 billion people, or 1 in 6 of the world's population, are adolescents aged 10–19. Adolescence is the second growth spurt of life and poses lots of challenges for the adolescent, parents, and caregivers. It marks a transition characterized by physical, emotional, and social changes. It is one of the most crucial and challenging periods of life with peak intelligence and stamina. The physical changes that herald adolescence are – the development of breasts, axillary and pubic hair, and first menstrual periods for girls and deepening of voice and broadening of shoulders for boys, which are the most striking markers of this stage. Developing brains bring new cognitive skills that enhance their reasoning ability and abstract thinking but these changes occur few years later than the physical development which brings in challenges for the adolescents and their caregivers. Adolescents develop cognitively, physically, socially, and emotionally. It prepares them to experiment with new behaviors. There is a high chance of adolescents getting into smoking, alcohol, and drug abuse. Changing sexuality predisposes for early unprotected and premarital sex. Some of the reasons for high- risk behavior in adolescents includes Living in increasingly sexualized societies, impact of media, rapid growth of cities, and breakdown of traditional family structure. HEADSS criteria are the best way to assess the characteristics of an adolescent (1) H – Home, (2) E - Education and employment, (3) A – Activity, (4) D – Drugs, (5) S – Sexuality, (6) S – Suicide/depression. Adolescents (20%) are important asset to our nation. Pediatricians with a little training can deal with the adolescent in a comfortable way.

Keywords: Understanding and dealing adolescents, Physical, Emotional and social changes, High-risk behavior in adolescents, HEADSS pediatrician

INTRODUCTION

Adolescents are one-third of the country's population and dealing with adolescents is not a child's play. According to the WHO, around 1.2 billion people, or 1 in 6 of the world's population, are adolescents aged 10–19.

UNDERSTANDING ADOLESCENCE

Adolescence is the second growth spurt of life and poses lots of challenges for the adolescent, parents, and caregivers. It marks a transition characterized by physical, emotional, and social changes. It is one of the most crucial and challenging periods of life with peak intelligence and stamina. This period plays a key role in the adolescence and it is the time for achievement, deciding profession, developing personality, etc. It is the most wonderful yet stressful period of life with emotional instability, lack of self-control, lots of societal, parental, and peer pressure.

The physical changes[1] that herald adolescence attain – the development of breasts, axillary and pubic hair, and deepening of voice and broadening of shoulders for boys, and first menstrual periods for girls, are the most striking markers of this stage. However, these physical changes represent just a fraction of the developmental processes that adolescents experience. From the teen's perspective, puberty puts a bright spotlight on body image which is the picture of physical appearance that they hold in their minds. It is normal for young people to feel conscious about their appearance. Once in a while, more serious difficulties arise as teens deal with physical changes.[2] These include fear, confusion, or withdrawal, obsessive concern about appearance, excessive dieting or exercise, experiencing depression and eating disorders, being bullied, teased, or excluded. Understanding the changes – developmentally and knowing what is happening and why – can help both adults and teens enjoy the second decade of life.

Their developing brains bring new cognitive skills that enhance their reasoning ability and abstract thinking but these changes occur few years later than the physical development which brings in challenges for the adolescents and their caregivers. Studies[3] using MRI analysis indicate that a wave of overproduction of gray matter – the thinking part of the brain – occurs just before puberty. This thickening of gray matter peaks at around age 11 in girls and 12 in boys, after which the gray matter actually thins somewhat. Previously, it was thought that the brain's wiring undergoes just one bout of "pruning" that was finished by the age of 3, but recently researchers have discovered that structural changes occur in adolescence and that teens gray matter waxes and wanes in different functional brain areas at different times in development. Brain development continues up to 25 years.

As adolescents develop their cognitive skills, however, some of their behaviors may be confusing to the adults who interact with them. Yes… It's Normal for Adolescents to Argue for the sake of arguing, jump to conclusions, be self-centered, constantly find fault and be overly dramatic. There are a number of ways that adults can help adolescents to make better decisions. One is to help them expand their range of options so they can consider multiple choices.[4] Adults can foster the development of adolescents' sense of competence.

As adolescents develop in various aspects such as – cognitive, physical, social, and emotional, it prepares them to experiment with new behaviors. There is a high chance of adolescents getting into smoking, alcohol, and drug abuse. Changing sexuality predisposes for early unprotected and pre-marital sex. Some of the reasons for high-risk behavior in adolescents living in increasingly sexualized societies, impact of media, rapid growth of cities, and breakdown of traditional family structure. Adults must become comfortable talking with adolescents or seek professional help for decision-making in these sensitive areas such as – sex, drugs and alcohol, and other safety concerns. The goal is to help the adolescent weigh the dangers and benefits of a particular situation, consider his/her own strengths and weaknesses that may affect decision-making and then make the best decisions possible. Factors associated with positive outcome are stable and positive relationship with at least one caring adult, religious and spiritual anchors, positive family environment, emotional intelligence, and ability to cope with stress.

THE FOLLOWING WERE THE MANAGEMENT OF ADOLESCENT PROBLEMS INCLUDES HEALTH SCREENING AND MANAGEMENT

1. Screening for adult onset diseases, screening and managing anemia and malnutrition, screening for refractive errors, deworming, thyroid disorders, and management of medical problems including growth and pubertal issues
2. Answering cosmetic queries, skin care including acne, hair care including dandruff, excessive hair growth, pigmentation, scars, liposuction, and plastic surgery
3. Management of S.T.D's and H.I.V's
4. Sexual and reproductive health empowering adolescents with responsible sexual behavior – abstinence, safe sexual practices, etc.
5. Adequate information and guidance about common concern
    - Knowledge about handling their growing bodies without harming others and not getting victimized to abuse
    - Concept of healthy relationships with peers, opposite sex, parents, teachers, etc.
    - Awareness about legal issues – age for marriage, consent for abortions, driving, alcohol, social networking, and child labor including domestic work
    - Rights and responsibilities – Right for education, information, privacy, confidentiality, right to health and life, and no gender discrimination.
6. Management of unwanted pregnancies in both married and unmarried.

DEALING WITH PARENTS – THEY ALSO NEED HELP

Authoritative type of parenting (both parent and adolescent are assertive and scope for reasoning, love, and warmth) is the need of the hour. Parents need to trust, empathize, and give unconditional love. Consistent disciplinary methods are extremely necessary. The channel of communication needs to be open.

DEALING WITH ADOLESCENT – EMPOWERING PEDIATRICIAN

1. Pediatrician should empower themselves with knowledge about adolescent growth development and concerns
2. Pediatricians should follow WHO adolescent-friendly criteria
   - Ensure privacy
   - Confidentiality
   - Non-judgmental.
3. Art of communication (adult to adult communication should follow with open-ended questions)
4. Consent and assent of both parents and adolescent should be taken (separate time should be given to adolescent)
5. Screening for HEADSS criteria – every pediatrician should take detail history including menstrual history and follow heads criteria for psychosocial screening
6. Taking the BP and BMI and checking for anemia and malnutrition, screening for refractive errors, deworming, thyroid disorders, and management of medical problems including growth and pubertal issues.

TIPS FOR TALKING WITH ADOLESCENTS

The following were some of the tips while talking with adolescent – Engage adolescents with nonthreatening questions. Listen non-judgmentally. Ask open-ended questions. Casually model rational decision-making strategies. Discuss ethical and moral problems without challenging his or her point of view. Active listening is very important while talking with adolescents.

HEADSS criteria are the best way to assess the characteristics of an adolescent. The following are the components:

1. H – Home
2. E – Education and employment
3. A – Activity
4. D – Drugs
5. S – Sexuality
6. S – SUCIDE/DEPRESSION

It is also important to seek professional help whenever necessary. Such help can be sought at centers like YUVA, The future…An Information, Guidance and health center for teens (10–19 years) established at Niloufer Hospital, Hyderabad, Telangana, or trained pediatricians in public or government sector.

Key points

1. Adolescents (20%) are important asset to our nation
2. Adolescent-friendly centers are needed to take care of their special health needs
3. All doctors and pediatrician can extend help to the adolescents with little training.

Declaration of patient consent

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Karnataka Pediatric Journal

Review Article

Oscillometry – The future of estimating pulmonary functions

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ABSTRACT

The prevalence of asthma is increasing rapidly, worldwide, due to changing gene-environment interactions. The rate of rise is more in resource poor nations due to lack of knowledge and non-availability of expertise. Monitoring of lung functions is mandatory for diagnosis and further management of asthmatic patients. Spirometry, the widely available investigation, is the gold standard test used for mapping pulmonary dynamicity. It has got its own limitations in the form of operational difficulties in children, the elderly, and in those with neuromuscular or behavioral issues. In the current era of COVID-19 pandemic, the utility of spirometry has been further restricted to selected cohort only, due to potential risk of viral transmission during the procedure. Oscillometry technique has been used previously, to monitor lung functions, with promising results. Ultrasonic waves of various frequencies accompany the tidal breath of patients and respiratory impedance is calculated by measured pressure and flow signals from exhaled breath. The results are interpreted in the form of resistance, reactance, resonant frequency, and reactance area. Various manufacturers have developed different mechanical models with slight variation in impulse pattern till date. There are certain distinct advantages of oscillometry over spirometry. Being tidal breath-based maneuver, it is more child friendly. People with neuromuscular weakness, cognitive limitations, and the elderly can easily perform it with only minor understanding and effort. Oscillometry is more sensitive than spirometry in detecting peripheral airway diseases. Post-bronchodilator reversibility can be evaluated by comparing with the baseline respiratory characteristics. Their utility in restrictive diseases and vocal cord dysfunction has also been explored. Less aerosol generation during the normal tidal breath is another advantage of oscillometry, over spirometry needing forceful efforts, which makes it more suitable for use in viral pandemic situations for monitoring patients with both asthma and pneumonia. More research is needed, in various geographic locations and heterogeneous populations, to devise the normative data of oscillometric parameters. Simultaneously, there is an urgent need for standardization of available machines at global platform.

Keywords: Oscillometry, Spirometry, Pulmonary function test, Respiratory impedance, COVID-19

INTRODUCTION

Allergic disorders are increasing worldwide with substantial affliction toward developing countries.[1] The current global prevalence of diagnosed asthma cases is 300 million.[1] In India, about 30% of the population is affected by some form of allergy.[2] Asthma prevalence has increased many folds over the past 6 decades and is currently influencing 15% of people in Indian capital.[3] As per a recent estimate, approximately half of the children present to a physician with at least one episode of wheezing by their sixth birthday.[4] These figures are underestimate of real quantity due to lack of awareness among health-care providers and non-availability of reliable diagnostic modalities in resource poor nations.[3] Demonstration of reversible airflow obstruction is desired in any patient with features of chronic airway inflammation (such as recurrent wheeze, breathlessness, chest tightness, and cough of variable intensity) for making a diagnosis of asthma.[5] Spirometry

is considered gold standard technique for demonstrating airway reversibility in suspected cases.[6] Although universally accepted, this modality has practical difficulties such as requirement of patient cooperation and forceful respiratory efforts.[6] It is cumbersome in young children, the elderly, patients with neuromuscular weakness, post-cardiothoracic surgery, and those with learning problems.[7,8] Finkelstein *et al*., in a multicentric survey, demonstrated that only 21% of 671 primary care physician used spirometry, due to operational dilemmas.[9] About 28% of people were either missed or overdiagnosed in another study using this tool.[10] Inability to reliably diagnose peripheral airway and parenchymal diseases are other shortcomings of this age-old technique.[10] Spirometry is not dependable in under-five wheezers.[5] With the emerging global problem of asthma, we urgently require a competent method which can overcome many of these shortcomings. An ideal lung function test should be possible at any age, safe, simple to perform, reproducible in different circumstances, and sensitive enough to detect minor changes in respiratory mechanics.[11]

Any technique based on tidal breathing would be ideal, especially in pediatric age group, where the cooperation expected from the subjects is minimal. Among the various available diagnostic modalities, some are oscillometry, interrupter technique, and body plethysmography.[12] Oscillometry seems a reasonable option to determine pulmonary mechanics in patients who are unable to perform spirometry.[13] It works on the principle of moving sound waves over tidal breath during the respiratory cycle. Resistance and reactance are calculated from measured changes in pressure and flow at different frequencies. Oscillometry is better in children and can provide additional information in adults for monitoring lung functions compared to spirometry.[14] Oscillation principle has been used previously in both pre-school and school-aged children to assess lung functions.[15] Gupta *et al*. have recently demonstrated airway reversibility using this technique in children as young as 2 years of age.[16] Patients with physical and cognitive limitations were also able to perform this maneuver convincingly.[17] Komarow *et al*. have explored its utility in identifying vocal cord dysfunction.[18] Another key highlight is reduced aerosol generation in oscillometry, which makes it a safer alternative in COVID-19 pandemic.[19]

HISTORICAL PERSPECTIVE

Oscillations were first used to quantify the mechanical behavior of respiratory system by Dubois *et al*. in 1956.[13] The approach commonly known as forced oscillation technique (FOT), in which airway characteristics in the form of impedance were monitored using sound waves of various frequencies. There have been several modifications in FOT over the past 6 decades with regard to configuration, oscillation type, frequencies, and assessment of airway parameters.[20] One such development, known as impulse oscillometry (IOS), was demonstrated by Michaelson *et al*. in 1975 using multiple frequencies at one point of time.[21] Oscillometry provides a detailed description of pressure-flow relationships over discrete frequencies. This provides a better insight about resistance and reactance of respiratory system than conventional spirometry.[8]

TYPES

Depending on the type of oscillation signals used, this technique can be classified as:[22]

- Monofrequency using single sinusoidal pressure waveform
- Pseudorandom noise (PRN) where impulses of several frequencies are simultaneously applied
- IOS in which recurrent impulses (square waveform) applied at a fixed frequency of 5 Hz.

Single frequency impulses are useful for monitoring patients with sleep apnea or those on mechanical respiratory support (ventilation or continuous positive airway pressure). PRN FOT impulses are widely used for monitoring various obstructive (asthma, bronchitis, and emphysema) and restrictive (interstitial lung disease, pulmonary fibrosis, and thoracic wall abnormalities) diseases. Intrabreath changes are better defined using recurrent impulses. Dandurand *et al*. have demonstrated that devices with PRN FOT signals are better in measurement of peripheral lung characteristics, than others, when subjected to higher mechanical load.[23]

The commonly used commercially available machines working on PRN impulses are Wave Tube, TremoFlo C-100, MostGraph-02 prn, and Resmon Pro, whereas Master Screen IOS and MostGraph-02 imp work with recurrent impulses.[23] The two most commonly available FOT models, Master Screen IOS and Resmon Pro, use 5, 10, and 20 Hz and 5, 11, and 19 Hz frequencies, respectively, to study the airway mechanical properties.[23]

PRINCIPLE

Oscillations of different frequencies are used to study respiratory impedance in FOT. The technique requires only passive cooperation from the patients for the evaluation of lung functions.[24] Respiratory impedance (Z) is a measure of resistive, inertial, and elastic forces of lungs and thoracic cage.[25] Sound waves of multiple frequencies, generated by a loud speaker, are superimposed over tidal breath of subjects through the respiratory system [Figure 1].[8]

These sound waves, being the mini pressure waves, cause subtle pressure changes in the airway which leads to change in airflow.[24] Smaller frequencies (2–4 Hz) can travel till the depth of lung peripheries, whereas higher frequencies (>20 Hz)

reach to proximal conducting airways only.[26] Middle range frequencies (5–20 Hz) are commonly used in clinical practice to determine respiratory characteristics [Figure 2] using fast Fourier transform technique.[14] Frequencies less than 5 Hz get easily altered by harmonics of the normal breathing,[26,27] whereas larger frequencies (>30 Hz) cause subjective discomfort and are affected by shunting properties of upper airways.[26,28]

The sound wave signals of pressure and flow are separated from the breathing pattern, by signal filtering mechanism, while returning from lungs during exhalation. The complex ratio of sinusoidal pressure (P) and flow (Q) for individual sound wave frequency, as determined by the pressure and flow transducers (pneumotachograph) at the mouthpiece, informs about the impedance of various segments of the respiratory system [Figure 1].[25] Impedance is calculated at discrete frequencies by ohm's law.

$$Z(\omega) = P(\omega)/Q(\omega)$$

$$\omega = 2.\pi.f$$

Where, Z – Impedance, P – Pressure, Q – Flow, ω – oscillation frequency function, f – frequency

Measured impedance (Z) is the sum of opposing forces in the respiratory system, resistance (R), and reactance (X). Z, calculated at individual frequency, informs about the mechanical properties of respective portion of airways [Figure 2].

TERMINOLOGY

- Impedance (Z) – It is defined as sum total of all the resistive, inertial, and elastic forces of respiratory system which a pressure impulse has to encounter during its travel through the respiratory system. It can be represented by a combination of resistance (R), a real force, and reactance (X), an imaginary component. Resistance and reactance are associated with energy dissipation and storage, respectively[25]

$$Z(\omega) = R(\omega) + jX(\omega)$$

R – Resistance, j – unit imaginary number defined as $\sqrt{-1}$, and X – Reactance

- Resistance (R) – It is a measure of opposition to airflow. It is directly proportional to length and inversely proportional to fourth power of radius of conducting tubes. Resistance measured at a particular frequency (f) is labeled as R_f, for example, R_5 is resistance detected at 5 Hz. R_f includes the resistance of oropharynx, larynx, trachea, large and small airways, lungs, and chest wall tissue
- Reactance (X) – Reactance can be understood as rebound resistance produced by distensible airways.[29] It is an imaginary component of impedance, which is defined by balance between inertance (I) (positive force) of conducting airway and capacitance (C) (negative force) of pulmonary parenchyma. Capacitance is in inverse correlation with elastic properties of lung

$$X(\omega) = \omega.I - E/\omega$$

$$X(\omega) = \omega.I - 1/\omega.C$$

$$X \propto I \quad X \propto C$$

Where, X – Reactance, I – Inertance, E – Elastance, and C – Capacitance

- Reactance measured at a particular frequency (f) is labeled as X_f, for example, X_5 is reactance at 5 Hz. At lower

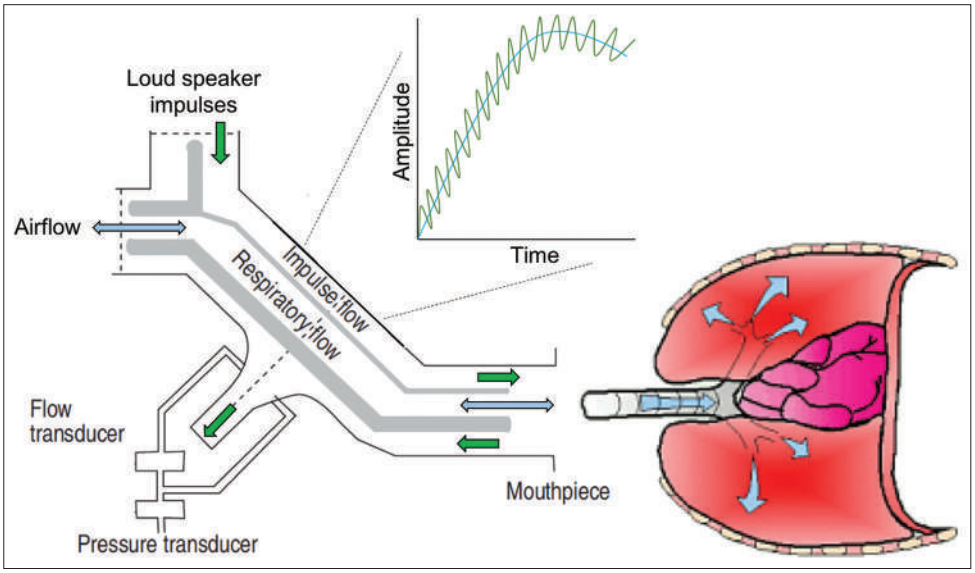

Figure 1: Principle of oscillometry. Sound waves (green) are superimposed over the normal tidal breath (blue) during respiration. Transducers measure the pressure and flow during exhalation for individual frequency which is utilized to calculate impedance of the respiratory system.

frequency, reactance is negative due to predominant capacitative forces, whereas it becomes positive toward higher frequencies, with major contribution from inertial forces [Figure 3]

- Resonant frequency (Fres) – It is the arbitrary frequency number at which capacitative and inertial forces equalize and reactance becomes zero [Figure 3]. Elastic forces dominate below Fres, whereas airway inertance plays major role above Fres.[29] Fres is usually higher in children and reduces with age
- Reactance area (Ax) – It is the triangular area limited by Fres (on right side) and reactance at 5 Hz (on left side) [Figure 3]. Ax provides information regarding peripheral airways and lung parenchyma. It is more sensitive parameter than Fres and X_5 (in descending order) for the detection of small airway obstruction as well as to document the bronchodilator reversibility
- Coherence – It is a quality control parameter which reflects the reliability of oscillometry maneuver. The value depends on relative comparison between input (flow) and output (reflected pressure) in the respiratory system.[30] Coherence values of >0.8 at 5 Hz and >0.9–1 at 20 Hz are considered satisfactory in adult subjects but cutoffs are yet to be validated for children.[15,31] The potential problem in relying on coherence is varied approaches used for calculations leading to different values by different manufacturers. Coherence values are reduced in pathological conditions or due to improper technique including swallowing, glottis closure, tongue causing airflow obstruction, and irregular breathing during the oscillometry maneuver.[32] High coherence values cannot rule out measurement errors or artifacts.[32]
- Coefficient of variation (CoV%) – This should be used over coherence to determine quality control, whenever available. CoV should be ≤10% in adults and ≤15% in children for two sets of R_5.[32]

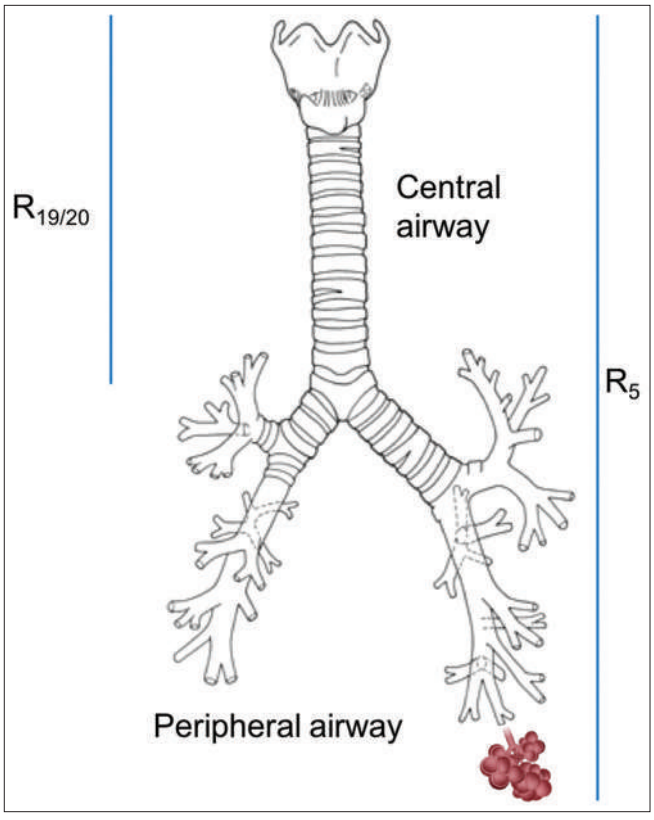

Figure 2: Impulses of various frequencies traveling through airway. Smaller frequency sound waves (5 Hz), being more energetic, travel till the farthest point of respiratory system, that is, alveoli. Higher frequency (20 Hz) remains in the central airways depicting the characteristic of respective part.

TECHNIQUE

Calibration of the machine, at least once a day, is desired with the external resistor or as per the manufacturer's specifications.[11] Bronchodilator medications (short-acting β-2 agonist for 4 h and long-acting β-2 agonist for 24 h) should be stopped before the procedure. After explaining the procedure (preferably by recorded video demonstration) to patient and attendants, anthropometric measurements (weight, height, and body mass index) are documented. Demographic (name, age, gender, area of residence, and identification number) and anthropometric parameters are entered in the machine after calibration. Patient is asked to sit on an examination stool/chair, with uncrossed legs to reduce the influence of extrathoracic pressure with straight

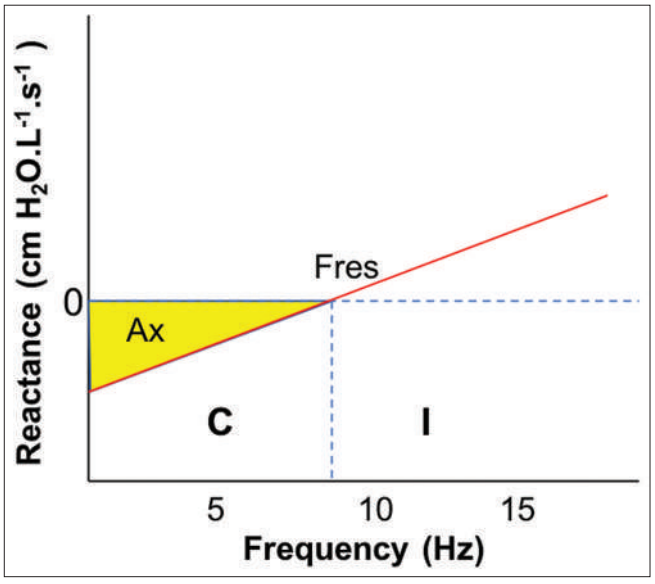

Figure 3: Changes in reactance with frequency. Fres: Resonant frequency, Ax: Reactance area, C: Capacitance, I: Inertance.

back [Figure 4].[30] He/she is asked to hold the mouth piece with his/her teeth and to make a tight seal around it with lips to prevent any air leak during the FOT maneuver. A nose clip is applied to occlude both the nostrils and he/she is asked to breathe through mouth piece. Height of sitting stool/chair and/or mouth piece is adjusted to achieve a comfortable position for the patient with slight neck extension. As FOT is based on small pressure oscillations and a little change in resistance or air leak can affect the interpretations significantly, it is important to ensure adequate seal around nose and mouth piece. The cheeks, most compliant part of respiratory system in children, should be supported firmly either by patient him/herself or attendant to minimize wobbling [Figure 4].[20] After appropriate positioning, patient is asked to perform normal tidal breathing in a relaxed manner. An average of 10 respiratory efforts or 1 min, whichever is earlier, is required to assess the respiratory characteristics during any maneuver.[12] Acquisitions of minimum 30 s for adults and 16 s for children (<12 years of age) with at least three acceptable breaths are recommended.[32] Respiratory efforts meeting acceptability criteria [Table 1] are considered valid, whereas maneuvers with artifacts such as airflow obstruction by tongue or glottic closure, irregular breathing, coughing, crying, swallowing, and improper technique will be discarded by the machine. A maximum of three acceptable maneuvers are recorded and checked for coherence or CoV. Mean respiratory impedance (resistance and reactance), resonant frequency, and reactance area are documented. The procedure is repeated 15 min after inhaled short-acting β-2 agonist to identify any post-bronchodilator reversibility.

NORMAL VALUES

- Impedance – Several studies have provided reference values for respiratory characteristics till date.[20] The references might vary as per the ethnicity and the oscillation technique used in different machines.[26] The commonly used regression equations, by the machine, for calculating R and X based on height (H) in meters, weight (W) in kilograms, and age (A) in years are as follows:[33]

for men –

R_{men} = –0.2454. H+0.001564. W–0.00055. A+0.5919

X_{men} = 0.1479. H–0.000402. W–0.00022. A–0.1721

and for women –

R_{women} = –0.4300. H+0.00165. W–0.00070. A+0.9312

X_{women} = 0.2487. H–0.001700. W–0.00053. A–0.2158

Normative values from Indian populations need to be devised. Gupta *et al.* have recently demonstrated a negative correlation between oscillometry parameters with height followed by body mass index in Indian children, while evaluating airway reversibility in asthmatic patients.[16] There was no gender influence observed on any of the parameter.

- Resonant frequency – The normal values of Fres varies in between 6 and 12 Hz in healthy adults[8,34] and it tends to be more in children
- Reversibility – The recommended cutoffs for significant bronchodilator response in both adults and children are –40% in R_5, +50% in X_5, and –80% in Ax.[32] These values might vary with severity of disease and more studies are required before considering them as benchmark
- Degree of bronchoconstriction – Cutoffs for X_5 have varied from 50 to 80% and more studies are needed to provide reference values for specific populations.[32]

INTERPRETATION

- Resistance (R) – Total, large/central, and small/peripheral airway resistances are represented as R_5, $R_{19/20}$, and R_5–$R_{19/20}$. R_5 is always higher than $R_{19/20}$. This difference is practically negligible in adults, whereas

Figure 4: Technique of performing oscillometry.

Table 1: Acceptability criterias – All of the following are required.

Domain	Criterias
Patient position	Sitting position at comfortable height Back straight with slightly extended neck Legs uncrossed Nose clip on Cheek firmly supported
Patient-machine interface	Tight seal around mouth piece No artefact due to irregular breathing efforts, tongue obstruction, speaking or coughing during maneuver, glottis closure or swallowing

it increases in younger children due to significant contribution by peripheral airway resistance. In peripheral airway obstruction, R_5 will increase with normal $R_{19/20}$ (and higher R_5–$R_{19/20}$) making frequency dependent airway resistance (R α 1/f).[24] In larger airway obstruction, both R_5 and $R_{19/20}$ will rise equally (with normal R_5–$R_{19/20}$), which will be frequency independent [Figure 5]. There will not be any change in restrictive lung diseases [Table 2]

- Spiky pattern in inspiration, demonstrated by >2 standard deviation variation in subsequent efforts at 5 Hz, may suggest vocal cord dysfunction.[18] The finding needs to be supported with further research
- Reactance (X) – It is usually measured at 5 Hz and becomes more negative in both peripheral airway obstruction and lung parenchymal disease [Figure 5]. It is not affected by large airway obstruction
- Resonant frequency (Fres) – It increases (shift to right) in both restrictive and peripheral airway obstructive diseases.[24] It is not affected by large airway obstruction
- Reactance area (Ax) – It increases in both small airway obstruction and restrictive diseases.[8] It is not affected by central airway problems.

COMPARISON WITH SPIROMETRY

Oscillometry is more sensitive for the detection of peripheral airway obstruction and restrictive diseases affecting lung parenchyma.[11,12] [Table 3] highlights the salient differences between spirometry and oscillometry.[8]

Use of spirometry has been restricted in current COVID-19 pandemic due to reasons of enhanced risk of disease transmission by potential aerosol generation.[35] Forced breathing maneuver causes more aerosol generation due to "airway reopening phenomenon."[36] Breathing till residual volume will reopen the collapsed alveoli causing increased air turbulence, leading to more production and release of smaller particles.[36] A small volume tidal breath, as used in oscillometry, will not cause much disturbance in the internal milieu and thus safeguarded in situations of active infections (such as influenza and corona). Gupta *et al*. have highlighted this concept recently, which suggest oscillometry procedure safer than spirometry in viral pandemic situations.[19]

CLINICAL APPLICATIONS OF OSCILLOMETRY

- Provides practically useful information regarding the subtle changes in airways with greater sensitivity, in both

Table 2: Changes in oscillometry parameters during pathological conditions.

Conditions	R_5	$R_{19/20}$	$R_5 - R_{19/20}$	X_5	Ax	Fres
Peripheral obstruction	↑↑↑	N	↑↑	More negative	↑↑	↑↑
Central airway obstruction	↑↑	↑↑	N	N	N	N
Combined airway obstruction	↑↑↑	↑↑	↑	More negative	↑↑	↑↑
Restrictive lung disease	N	N	N	More negative	↑↑	↑↑

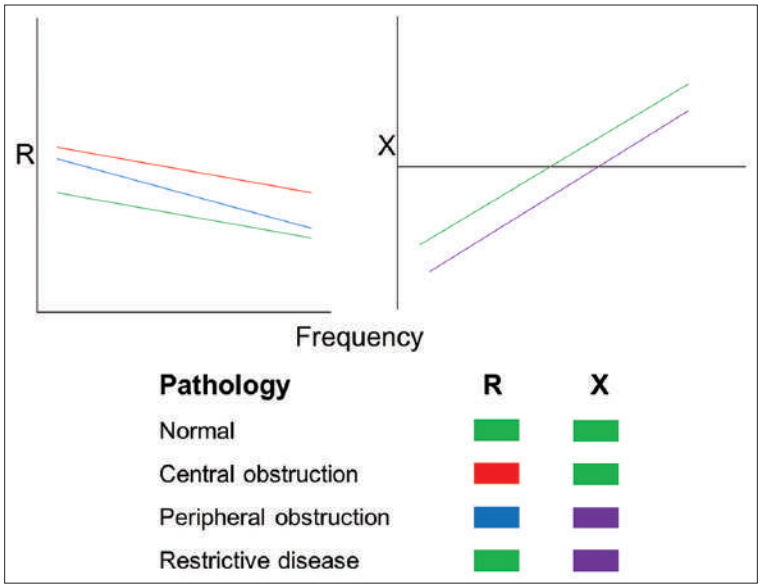

Figure 5: Respiratory characteristics in health and disease. R – Resistance (in cm $H_2O.L^{-1}.s^{-1}$), X – Reactance (in cm $H_2O.L^{-1}.s^{-1}$). During normal healthy conditions, the resistance and reactance are at baseline (green). Various combinations of changes in these parameters will help in determining the nature and location of pathology.

children and adults, when compared to spirometry[37,38]
- Useful to assess abnormal distal airway function, in case of clinical suspicion with normal spirometry[38,39]
- Bronchodilator reversibility can be demonstrated with short-acting β-2 agonists and ipratropium[40,41]
- Good potential in diagnosis and monitoring of restrictive lung diseases such as bronchopulmonary dysplasia,[42] cystic fibrosis,[43] and interstitial lung disease[44]
- Feasible option in children, the elderly, and those with neuromuscular diseases and impaired intellect[24,26]
- Potentially useful in patients on mechanical ventilation[45] and during sleep[11]
- Safer than spirometry during viral pandemic situations (e.g., influenza and corona) due to less aerosol generation.[19] Oscillometry can be used to reliably diagnose and monitor patients with asthma and COVID-19 pneumonia.

[Figure 6] shows an algorithmic approach to a patient with oscillometric lung function assessment.

Table 3: Comparative analysis between spirometry and oscillometry.

Parameter	Spirometry	Oscillometry
Principle	Measures flow rates and lung volumes	Calculates impedance by measuring flow and pressure of sound waves
Parameters measured	FEV_1, FVC, PEFR, $FEF_{25-75\%}$	Z, R, X, Fres, Ax
Type of breath required	Forced maneuver	Tidal breath
Patient cooperation needed	High	Minimal
Can be performed in children	>7 years	>2 years
Patients with neuromuscular weakness, intellectual disability, post cardiothoracic surgery	Procedure cannot be done	Can be done
Sensitivity for detection of peripheral airway obstruction	Low	High
Aerosol generation	High	Very low
Standardization of method	Yes	Yet to be done
References value	Available	Need more studies

FEV_1 – Forced Expiratory Volume in 1 second, FVC – Forced Vital Capacity, PEFR – Peak Expiratory Flow Rates, $FEF_{25-75\%}$ - Forced Expiratory Flow at 25-75% of FVC, Z – Impedance, R – Resistance, X – Reactance, Fres – Resonant frequency, Ax – Reactance area

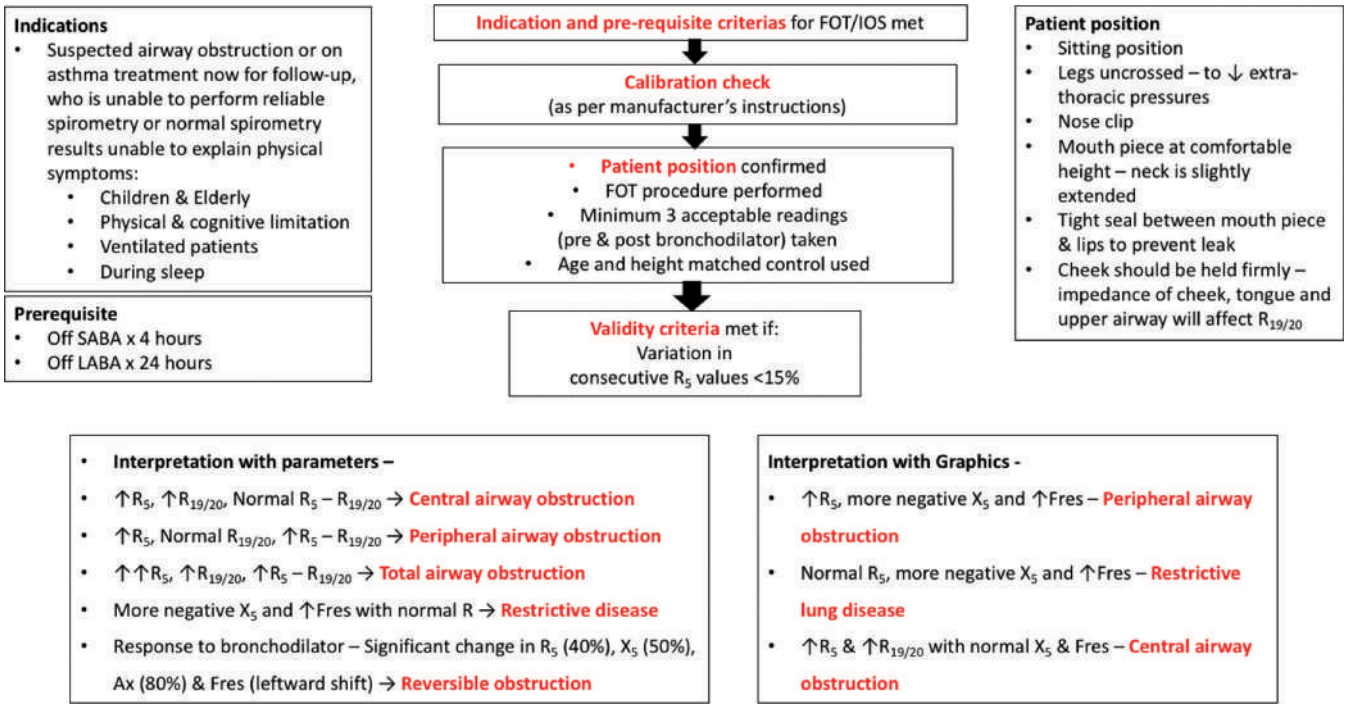

Figure 6: Approach to a patient with oscillometric assessment. FOT: Forced oscillation technique, IOS: Impulse oscillometry, SABA: Short-acting β2 agonist, LABA: Long-acting β2 agonist, R: Resistance (in cm $H_2O.L^{-1}.s^{-1}$), X: Reactance (in cm $H_2O.L^{-1}.s^{-1}$), Fres: Resonant frequency (in Hz), Ax: Reactance area.

Limitations

- Although this technique is tidal breath based, still a minimum amount of cooperation is needed from patients
- Standardization of the available machines with different manufactures is needed
- Reference values for different populations are not available
- Reference cutoff values for bronchodilator reversibility need to be validated with more studies
- Poor cheek support can reduce the resistance values[46]
- More research required in restrictive diseases, ventilated, and/or sedated patients and patients with vocal cord dysfunction.

CONCLUSION

Oscillometry, being a tidal breath-based technique, can be a real privilege to physicians and their patients for monitoring lung functions. It is more sensitive in detecting small airway pathologies than conventional spirometry. Limited aerosol generation could be another reason for its use in viral pandemics for monitoring lung functions. More research is required for identifying regional reference values and standardization of machines.

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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Review Article

Clinical approach to renal tubular acidosis in children

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ABSTRACT

Renal tubular acidosis (RTA) is a common inherited tubulopathy in children. Proximal RTA, usually secondary to a systemic metabolic disease, is characterized by a generalized dysfunction of the proximal tubule resulting in Fanconi syndrome. Distal RTA occurs due to mutation in the transporters of the distal tubule resulting in acidification defects. Hyperchloremic metabolic acidosis with normal anion gap is the characteristic feature of RTA. In addition to supportive therapy, specific treatment for the underlying etiology and regular monitoring of growth and laboratory parameters are of utmost importance.

Keywords: Renal tubular acidosis, Children, Fanconi syndrome, Distal renal tubular acidosis

INTRODUCTION

The kidneys play a key role in preserving the acid–base homeostasis in the body by excretion of acid and regeneration of bicarbonate. Renal tubular acidosis (RTA) arises from the kidney's inability to excrete enough acid or retain enough bicarbonate, in the presence of normal renal function, resulting in a clinical syndrome characterized by persistent normal anion gap hyperchloremic metabolic acidosis.[1,2]

ACID–BASE HOMEOSTASIS: ROLE OF THE KIDNEY

Bicarbonate reabsorption in the proximal tubule

The proximal tubule is responsible for reabsorption of 85–90% of filtered bicarbonate through secretion of protons (H^+) through the sodium hydrogen exchangers and proton pumps (H^+ATPase).[1,3] In the lumen, the secreted hydrogen ions combine with HCO_3^- to form carbonic acid which rapidly dissociates into carbon dioxide and water, a reaction catalyzed by carbonic anhydrase. The carbon dioxide generated diffuses freely into the proximal tubule cell and reacts with water to form carbonic acid, a reaction catalyzed by carbonic anhydrase (CA II). Bicarbonate ions from the dissociated carbonic acid exit through the basolateral membrane by the sodium bicarbonate exchanger (NBCE1)[4,5] [Figure 1].

Urinary acidification in the distal tubule

The acidification of urine occurs in the distal collecting tubule and collecting duct. The intercalated cells A (secrete H^+), B (secrete HCO_3^-) and principal cells (reabsorb sodium, water, and secrete K^+) of the distal nephron play a pivotal role in fine tuning acid and base excretion.

The generated HCO_3^- is transported to the blood in exchange for chloride by the basolateral Cl^-/HCO_3^- exchanger. The hydrogen ions secreted into the lumen by intercalated cells A are buffered by titratable acids (phosphate) and ammonia and excreted in the urine[6] [Figure 2].

TYPES OF RTA

Type 1 RTA – distal RTA (dRTA)

dRTA, characterized by impaired hydrogen ion secretion in the distal tubules, is commonly seen due to inherited mutations of transporters in the distal tubule.

The hallmark of distal RTA is the inability to lower urine pH maximally in the presence of moderate-to-severe metabolic acidosis. Failure of the distal tubules to excrete the acid load generated by metabolism and in the growing bone in children leads to accumulation of acid and worsening base deficit. Extracellular bicarbonate and hydroxyapatite in the bones serve as buffers to neutralize the accumulated acid. Hypokalemia seen in RTA is due to proximal and distal wasting of sodium, leading to volume contraction and secondary hyperaldosteronism. It is more commonly associated with dRTA as potassium is the only available cation for exchange with sodium and distal secretion of H^+ is impaired. Hypercalciuria and hypocitraturia are seen in dRTA which make the children prone for early-onset nephrocalcinosis and nephrolithiasis.[7]

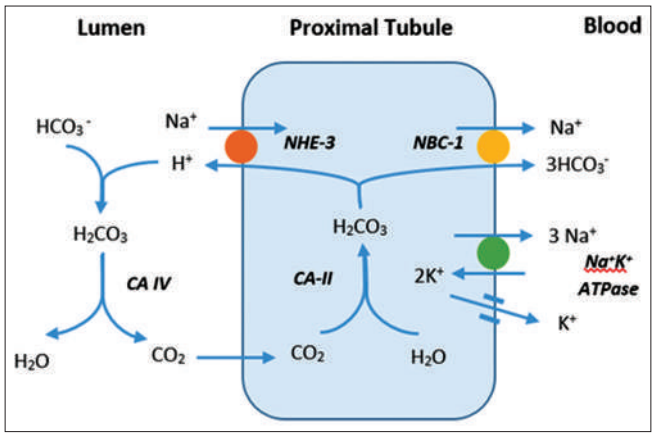

Figure 1: Bicarbonate reabsorption in proximal tubule.

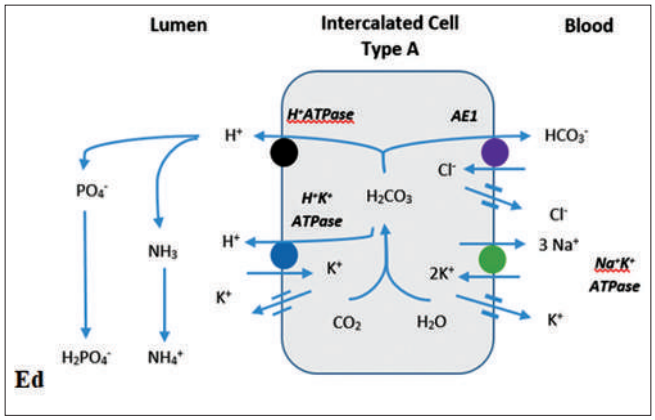

Figure 2: Distal urinary acidification. NHE 3: Sodium hydrogen exchanger 3, NBC-1: Sodium bicarbonate cotransporter, AE1: Anion exchanger, CA II: Carbonic anhydrase II, CA IV: Carbonic anhydrase IV.

Etiology

1. Inherited distal RTA[8]
   Refer to [Table 1].
2. Acquired dRTA
   a. Autoimmune – Sjogren's syndrome, systemic lupus erythematosus, and Graves' disease
   b. Medications – Amphotericin, lithium, and aminoglycosides.

Type II RTA – proximal RTA

Proximal RTA is caused by an impairment of bicarbonate reabsorption with intact distal acidification mechanisms and is characterized by decreased renal bicarbonate threshold (14–18 mEq/L), defect in ammonia generation, and ability to lower urine pH <5.5. Hypokalemia is commonly seen in proximal RTA.[9]

Etiology

Proximal RTA usually occurs in association with other tubular defects as a part of the generalized proximal tubular defect – Fanconi syndrome (inherited or acquired). Isolated proximal RTA is rare.

1. Isolated proximal RTA
   a. Genetic
      - Autosomal dominant
      - Autosomal recessive – with ocular abnormalities (NBCE1), CA II mutation.
   b. Inherited – CA II inhibitors
2. Fanconi syndrome[10]
   Fanconi syndrome is a generalized dysfunction of the proximal tubule resulting in hypokalemia, polyuria, bicarbonate wasting, glycosuria, low-molecular-weight proteinuria, generalized aminoaciduria, and phosphaturia resulting in hypophosphatemia.
c. Hereditary
   Refer to [Table 1].
d. Acquired causes
   - Autoimmune conditions – Sjogren's syndrome
   - Malignancy – Acute lymphatic leukemia, multiple myeloma
   - Medications – Valproic acid, acetazolamide, cisplatin, lamivudine, tenofovir, outdated tetracyclines,

Table 1: Hereditary causes of renal tubular acidosis.

Disorder	Inheritance	Gene	Chromosome	Protein	Extrarenal features
Distal RTA					
Autosomal dominant	Autosomal dominant	SLC4A1	17q21-q22	Anion exchanger	Hemolytic anemia
Autosomal recessive	Autosomal recessive	ATP6V1B1	2q13	H^+ATPase	Hearing impairment
		ATP6V0A4	7q33-q34		
Proximal RTA					
Cystinosis	Autosomal recessive	CTNS	17p13	Cystinosin	Eyes, CNS, endocrine
Dent's disease	X linked	CLCN5	Xp11.22	Chloride channel	Rare
Type I		OCRL1 (15%)			
Type II					
Fanconi-Bickel	Autosomal recessive	SLC2A2	3q26.1–q26.3	GLUT2	Hepatic
Galactosemia	Autosomal recessive	GALT	9p13	Galactose-1-phosphate uridylyltransferase	Eye, hepatic, CNS
Hereditary fructose intolerance	Autosomal recessive	ALDOB	9q22	Fructose-1 phosphate aldolase	Hepatic
Lowe syndrome	X linked	OCRL1	Xq26.1	Phosphatidylinositol 4,5-bisphosphate 5-phosphatase	CNS, eye
Tyrosinemia	Autosomal recessive	FAH	15q23-q25	Fumarylacetoacetate hydrolase	Hepatic
Wilsons disease	Autosomal recessive	ATP7B	13q14.3-q21.1	ATPase copper transporting beta-polypeptide	Hepatic, CNS, eye

RTA: Renal tubular acidosis, CNS: Central nervous system

aminoglycosides, Chinese herbs, heavy metals (lead, cadmium, mercury, and copper).

Type III RTA – mixed RTA

Type III RTA, an outdated terminology, has combined features of proximal and distal RTA. Association of Type III RTA with osteopetrosis has been commonly described with loss of function mutation of CA II.[11]

Type IV RTA – hyperkalemic RTA

In hyperkalemic RTA, the primary defect lies in the regeneration of bicarbonate secondary to lack of adequate urinary ammonia. This is seen in conditions with aldosterone deficiency or resistance.[12] The acquired causes of aldosterone resistance are the most common causes encountered in clinical practice.

Etiology

1. Hereditary
   a. Congenital hypoaldosteronism
   b. Pseudohypoaldosteronism.
2. Acquired
   a. Urinary tract – posterior urethral valve, reflux nephropathy, pyelonephritis
   b. Autoimmune conditions – interstitial nephritis
   c. Drugs – trimethoprim, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, angiotensin-converting enzyme inhibitors

CLINICAL CLUES TO SUSPECT RTA IN A CHILD

RTA must be suspected in any child who presents with

a. Failure to thrive
b. Resistant rickets
c. Polyuria, polydipsia
d. Salt craving – preference for salty foods
e. Symptoms of hypokalemia
f. Acidotic breathing
g. Nephrocalcinosis/nephrolithiasis.

In younger children, polyuria may manifest as recurrent episodes of dehydration in the absence of diarrheal losses, normal urine output in the presence of dehydration, or preference for water over other liquids. Hypokalemia may manifest as abdominal distension, muscle weakness – head lag, or a sudden onset of hypotonia/paralysis usually following an acute illness.

EVALUATION OF RTA[9,13]

The first step in the evaluation of RTA is the identification of hyperchloremic normal anion gap metabolic acidosis in the presence of normal renal function.[9]

a. Anion gap: The anion gap should be calculated by a simultaneous measurement of serum electrolytes and bicarbonate.

   Anion gap = $[Na^+ - (Cl^- + HCO_3^-)$
   Normal anion gap is 8–12 meq/L.

Anion gap may be affected by the serum albumin levels.

Corrected anion gap = calculated anion gap+ 2.5 (Normal albumin – measured albumin).

The two common conditions causing normal anion gap are diarrhea and RTA.

b. Urine anion gap

The urine anion gap is an indirect measurement of the urinary ammonia excretion in response to metabolic acidosis.

Urinary anion gap = $(Na^+ + K^+) - Cl^-$ (measured in the urine).

Normally, the urine anion gap is positive. In the presence of metabolic acidosis, the normal kidney is able to generate ammonium (NH_4^+) and excrete it along with Cl^-, making the urine anion gap negative. A persistent positive anion gap in the presence of metabolic acidosis is suggestive of a renal acidification defect.

Caveats: Urine anion gap estimates ammonium excretion only in chronic metabolic acidosis. If the urine pH>6.5, bicarbonate is excreted, hence, urinary anion gap does not reflect urinary ammonium levels.

c. Urine osmolal gap: This is used in situations where the urine anion gap is not reliable.

Urine osmolal gap = measured osmolality – calculated osmolality.

Calculated urine osmolality= $2[Na^+ + K^+]$ + urea + glucose 6 18

Urinary ammonium excretion is estimated to be half the urinary osmolal gap and is considered to be increased if it >100 mosm/kg.

Once, the diagnosis of RTA is confirmed, the next step is to differentiate between the different types of RTA[13]

a. Urine analysis: A routine analysis of urine for the presence of proteinuria (usually non-nephrotic range, i.e., urine albumin 1+–2+), glycosuria indicates the presence of generalized tubular wasting seen with Fanconi syndrome
b. Urine pH: A urine pH >5.5 in the presence of metabolic acidosis is suggestive of distal acidification defect seen with dRTA. If systemic acidosis is mild, it can be induced using the ammonium chloride loading test. Ammonium chloride is given at 0.1 mg/kg followed by measurement of urine pH every hour for the next 2–8 h. The total plasma CO_2 should fall by 3–5 meq/L and urine pH should be <5.5. Ammonium chloride loading test should not be performed in children with moderate-to-severe acidosis (serum bicarbonate <17 meq/L)

Caveat: The urine pH should be measured in a freshly voided sample of urine using a pH meter. The urine pH must always be interpreted with the urine sodium. Low urine sodium will result in low H^+ secretion

c. Fractional excretion of bicarbonate: Following a bicarbonate loading test (sodium bicarbonate 0.5 meq/ml is administered at 3 ml/min), measure the urine pH every 30–60 min till 3 consecutive samples show a pH >7.5.

The fractional excretion of bicarbonate is calculated

The normal fractional excretion of bicarbonate is <5%. A fractional excretion > 15% suggests bicarbonate wasting

d. Urine-blood PCO_2: After a load of sodium bicarbonate, the secreted H^+ reacts with the luminal HCO_3^- in the distal lumen forming carbonic acid. In the absence of CA II, this slowly gets converted to CO_2 which remains trapped in the lumen. At a urine pH>7.5 and serum bicarbonate 23–25 meq/L, the urine PCO_2 should be >70 mmHg. The urine-blood PCO_2 > 20 mmHg is seen with normal acid secretion. Urine-blood PCO_2<20 mmHg indicates a defect in distal acid secretion

Caveats: Urine for PCO_2 should be collected from a freshly voided sample in a sealed syringe using mineral oil and measured by a blood gas analyzer

e. Furosemide fludrocortisone test: The furosemide fludrocortisone test assesses the ability of the distal tubule to secrete acid. Furosemide increases the distal sodium delivery, which, in turn, enhances distal H^+ secretion. Fludrocortisone also increases H^+ secretion. After an overnight fasting, early morning pH is checked, if urine pH >5.5, oral furosemide is administered at 1 mg/kg and fludrocortisone at 0.025 mg/kg. Urine pH is measured hourly for 4–6 h. A urine pH <5.5 indicates an intact distal acidification mechanism.

Caveat: Ensure normal serum potassium before the test

f. Fractional excretion of phosphate: Fractional excretion of phosphate can be measured using a spot or timed urine sample along with simultaneously measured serum values. The normal fractional excretion of phosphate is 8–15%. Fractional excretion >15% suggests phosphate wasting.

The tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR) is a better indicator and can be calculated using the Bijvoet's nomogram or using the formula. Normal TmP/GFR is 2.8–4.4 mg/dL, which will be reduced in Fanconi syndrome.

g. Generalized aminoaciduria: Generalized aminoaciduria> 5% is suggestive of proximal tubular wasting
h. Low-molecular-weight proteinuria: Elevated levels of β2 microglobulinuria is suggestive of Fanconi syndrome

i. Urinary calcium creatinine ratio: The spot urinary calcium to creatinine ratio is increased (>0.2 in children >2 years of age) in distal RTA and some forms of proximal RTA like Dent's disease. A 24 h urinary calcium excretion >4 mg/kg/day is considered as hypercalciuria
j. Hypocitraturia – 24 h urine citrate is estimated using colorimetric methods. 24 h urine citrate levels of <2 mg/kg is termed as hypocitraturia
k. Ultrasound examination of the kidney – for nephrocalcinosis and nephrolithiasis – seen in distal RTA
l. Evaluation for extra-renal involvement – Eye examination could reveal cystine crystals in children with cystinosis. Assessment of hearing must be done in all children with dRTA.

The clinical and laboratory presentation of proximal and distal RTA is compared in [Table 2].

TREATMENT FOR RTA

Type I RTA

The goal of treatment is to correct metabolic acidosis, prevent bony deformity, and improve growth. Treatment for dRTA consists of alkali therapy to correct metabolic acidosis. Bicarbonate supplements (4–6 mEq/kg/day in infants to 2–4 mEq/kg/day in children), in the form of potassium citrate formulations, are recommended to ensure normal growth.[14] Hypokalemia improves with correction of acidosis, but some children require long-term supplements (1–2 mEq/kg/day). Potassium citrate in addition to correcting metabolic acidosis and hypokalemia provides citrate which reduces hypercalciuria. It must be remembered that these measures will not retard the progression of nephrocalcinosis or hearing impairment. Regular screening for nephrocalcinosis and hearing impairment must be done and targeted therapy instituted.

Type II RTA

The management of proximal RTA depends on the etiology of tubular dysfunction. The goal of supportive therapy is to promote growth and prevent bony deformities. The main stay of treatment is supplementation of urinary losses of bicarbonate with high doses of alkali (10–15 mEq/kg/day), potassium (1–5 mEq/kg/day), and phosphate (20-40 mg/kg/day). Sodium (3–5 mEq/kg/day) and magnesium (25–50 mg/kg/day) supplements may be needed in some children. Unlike dRTA, children with proximal RTA require high doses of bicarbonate therapy to sustain bicarbonate levels around the renal threshold. Commonly used bicarbonate supplements include:

- Syrups – Potrate (Bicarbonate and potassium 2 mEq/ml), Nodosis (0.8 mEq/ml)
- Tablets – Sodamint (3.6 mEq/300 mg, 6 mEq/500 mg, 7.8/650 mg), Acidose 500 mg.

Phosphate supplements (Addphos sachet 500 mg, K-Phos tablet 500 mg, and Joules solution 30 mg/ml) are administered at 20–40 mg/kg/day in 3–4 divided doses. The common side effects include diarrhea and abdominal pain. Active Vitamin D supplementation (calcitriol 20–40 ng/kg/day) with regular assessment of urine calcium and annual renal scan to monitor for nephrocalcinosis is recommended.[15] Nutrition in children with RTA is compromised due to polydipsia, polyuria with increased losses of sodium and other nutrients, and poor intake. Intake of calorie dense foods rich in potassium and phosphorus with adequate fluids is encouraged.

Hyperkalemic RTA

The primary treatment is to stabilize serum potassium concentration by stopping all potassium containing medications,

Table 2: Comparison of the clinical presentation and investigations of proximal and distal RTA.

	Proximal RTA	Distal RTA
Clinical presentation	Usually as a part of a systemic disease; most often metabolic disease	Usually isolated; autosomal recessive forms are associated with hearing loss
Bony deformity	Variable	Usually severe
Metabolic acidosis	Usually milder, but difficult to correct; requires high doses of bicarbonate supplementation	Severe acidosis; easily corrected with bicarbonate supplementation
Serum potassium	Normal/low	Low
Urine pH	<5.5	>5.5
Fractional excretion of bicarbonate	>15%	<5%
Urine-blood PCO_2	>20 mmHg	<20 mmHg
Phosphaturia and hypophosphatemia	Present (variable)	Absent
Tubular defects – low-molecular-weight proteinuria, aminoaciduria, glycosuria	Present (variable)	Absent
Hypercalciuria/nephrocalcinosis	Occasionally present	Often present

RTA: Renal tubular acidosis

restricting dietary sources, and addition of potassium-binding resins (calcium polystyrene sulfonate K-Bind 15 g sachets – 1 g/kg/day in 2–3 divided doses).[12] Bicarbonate supplement should be administered to correct acidosis.

SPECIFIC DISORDERS CAUSING RTA

Proximal RTA

Cystinosis

Cystinosis is the most common hereditary cause of Fanconi syndrome. It is an autosomal recessive lysosomal storage disorder resulting from a defect in the gene CTNS (SLC3A1, SLC7A9) encoding for cystinosin, a lysosomal cystine-proton cotransporter. The commonly affected organs include kidney, eyes, thyroid, pancreas, gonads, and central nervous system. The infantile nephropathic form is seen in 95% of all cases of cystinosis.[16] There is early onset of renal involvement with rapid progression to end-stage renal disease by the end of the first decade. Ocular (corneal deposits in 100% by 18 months), endocrine (50–70% hypothyroidism by the 2nd decade), gonadal (70% have primary hypogonadism), and central nervous system (encephalopathy in 45% by late second decade) involvement are common extrarenal manifestations.[17] Cystine depletion therapy with cysteamine delays end-stage renal disease but does not stop its progression.[18]

Tyrosinemia

Hereditary tyrosinemia Type I is an autosomal recessive inborn error of metabolism, due to deficiency of fumarylacetoacetate hydrolase, mainly affecting the liver and kidney during early infancy. Hepatic manifestations include abnormal synthetic function with coagulopathy, transaminitis, hypoglycemia, acute liver failure in the first few weeks to life, and progression to cirrhosis in early childhood. The spectrum of renal involvement varies in severity from hypophosphatemic rickets, generalized aminoaciduria, and proteinuria with occasional glucosuria (lower incidence in view of decreased plasma glucose levels) to long-term complications of glomerulosclerosis, nephrocalcinosis, and chronic kidney disease. Treatment with low phenylalanine and low tyrosine diet improves renal tubular dysfunction. An effective medical treatment with nitisinone (2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione) has optimal long-term preventive effects if initiated early and when plasma levels are maintained at 40–60 μmol/L.[19]

Dent's disease

Dent's disease is an X-linked hereditary form of Fanconi syndrome characterized by proximal tubular dysfunction – low-molecular-weight proteinuria, hypercalciuria, hypophosphatemic rickets, nephrolithiasis, nephrocalcinosis, and progression to end-stage renal disease. More than 50–60% of cases are attributed to mutations in CLCN5 gene (Dent I), 15% have mutations involving the OCRL1 gene (Dent 2). Extrarenal symptoms are rare in Dent's disease.[20] There is no specific treatment available to retard the progression to end-stage renal disease, which commonly occurs by 30–50 years of age.

Lowe syndrome

Lowe syndrome (oculocerebrorenal syndrome) is an X-linked disorder resulting from mutation in OCRL gene (encoding α-phosphatidylinositol 4, 5-biphosphate phosphatase). Bilateral cataract, generalized hypotonia at birth, and proximal RTA with progression to chronic kidney disease by the second decade are characteristic of Lowe syndrome. Treatment is primarily supportive and involves cataract removal, glaucoma control, targeted rehabilitation therapy, and correction of tubular dysfunction with supplements.[21]

Glycogen storage disorder (GSD)

GSD Type Ia is an autosomal recessive disorder with deficiency of glucose-6-phosphatase-α. Children with GSD I have failure to thrive, hypoglycemia with hepatorenomegaly, hyperuricemia, hyperlipidemia, and proximal RTA.

The other GSD with Fanconi phenotype is Fanconi Bickel syndrome, also referred to as GSD XI, which is caused by a deficiency of GLUT2 transporter, secondary to mutations in SLC2A2 and is characterized by failure to thrive, chronic diarrhea, fasting hypoglycemia, postprandial hyperglycemia, hepatomegaly, and proximal tubular dysfunction typically manifesting in infancy. Dietary modification with restriction of glucose and galactose with incorporation of cornstarch is the main treatment.[22]

Distal RTA

Autosomal dominant

Autosomal dominant distal RTA occurs due to heterozygous mutation of anion exchanger (AE1) in the basolateral surface of the Type A intercalated cells. The usual presentation is during adolescence with features of nephrocalcinosis, nephrolithiasis, occasional rachitic changes, and mild or compensated hyperchloremic metabolic acidosis. Hereditary spherocytosis and ovalocytosis can occur secondary to involvement of AE1 on the erythrocyte membrane.[23,24]

Autosomal recessive

Mutations in ATP6V1B1, ATP6V0A4, and SLC4A1 present in early infancy or childhood with failure to thrive, episodes of vomiting or dehydration, rickets, and nephrocalcinosis

with severe metabolic acidosis. These autosomal recessive distal renal tubular disorders are associated with early-onset bilateral sensorineural hearing loss in those with ATP6V1B1 mutations.[25]

Outcome

Proximal RTA secondary to cystinosis, Dent's disease, etc., have a relentless progression to chronic kidney disease. Although the clinical presentation of proximal tubular dysfunction may be variable, most causes of pRTA are associated with severe growth failure and bony deformities despite adequate treatment. The metabolic abnormalities are often hard to correct despite large supplementary doses.

Distal renal tubular dysfunction is often limited to the kidney alone. They rarely progress to chronic kidney disease. Growth impairment, bony deformities, and metabolic parameters are correctable with adequate therapy.

CONCLUSION

Children with renal tubular acidosis require a thorough evaluation to ascertain the etiology of RTA. Regular long-term follow-up and monitoring of growth, bony deformities and renal function is required.

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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Review Article

Polycystic ovarian syndrome in adolescence

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ABSTRACT

Polycystic ovarian syndrome (PCOS) may clinically manifest for the 1st time in adolescence. Hyperandrogenemia and oligo-anovulation are the two essential criteria for the diagnosis of PCOS. PCOS has long-term effects on cardiovascular, endocrinal, reproductive, and metabolic health. Early management of PCOS mitigates its long-term effects on health. Therapeutic lifestyle management and psychological counseling form the main stay of treatment in adolescence. Diagnosis of PCOS in adolescence is revisited and confirmed in adulthood. Management of PCOS is multidisciplinary and requires long-term regular follow-up in adolescence and adulthood.

Keywords: Polycystic ovarian syndrome, Adolescence, Hyperandrogenemia, Oligo-anovulation

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common female endocrinopathy. Clinical features of PCOS are usually evident in adolescence. Management in adolescence can mitigate the long-term effects of PCOS.

DIAGNOSIS OF PCOS IN ADOLESCENCE

It is difficult to make an accurate diagnosis of PCOS in the adolescent period using the conventional adult Rotterdam criteria that include the presence of two of the following: Oligo-anovulation, hyperandrogenism, and polycystic ovaries on ultrasound. All the three features are a part of normal growth and development in adolescence. Oligo-anovulation characterized by irregular periods is normal in the 1st few years after attaining menarche. About 80% of adolescents have acne. Severe acne that is resistant to treatment is a clinical indicator of hyperandrogenism. Multiple cysts in the ovaries are commonly seen on ultrasound in adolescence. An ovarian volume >12 cc in adolescence is considered by some researchers as a pointer toward PCOS.

The recently published International Guidelines state that both oligo-anovulation and hyperandrogenism should be present for diagnosing adolescent PCOS and polycystic ovaries on ultrasound are not considered as a diagnostic criterion.[1] Other causes of hyperandrogenism and anovulation have to be excluded before making a diagnosis of PCOS. These include congenital adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome, thyroid dysfunction, and hyperprolactinemia.

Ovulatory dysfunction clinically presents as irregular menstrual cycles. Oligo-anovulation in adolescents is defined according to the gynecological age (number of years after attaining menarche).

- For adolescents who are 1–<3 years post-menarche, the interval between menstrual cycles <21 days or >45 days is considered oligo-anovulation.
- For adolescents who are 3 years post-menarche, the interval between menstrual cycles <21 or >35 days or <8 cycles/year is considered oligo-anovulation.
- For adolescents 1 year post-menarche, duration of >90 days for any one cycle and if menarche is not attained by the age of 15 years or >3 years post-thelarche, it is considered oligo-anovulation.

Clinical diagnostic criteria for hyperandrogenism include severe acne and hirsutism in adolescence, as shown in [Figure 1]. Biochemical criteria of hyperandrogenism are increased calculated free testosterone and free androgen index. In adolescence, normal levels of testosterone are not well defined; hence, persistent testosterone elevation above adult norms is a reliable reference for hyperandrogenism. Longitudinal follow-up of suspected cases of PCOS in adolescence is recommended and the diagnosis is revisited at 8 years post-menarche.

PATHOPHYSIOLOGY

Pathophysiology of PCOS is not clearly delineated. Both genetic and environmental factors contribute to its development.[2,3] Inheritance is said to be both X linked and autosomal dominant. In most cases, there is a family clustering in female siblings and a positive family history of diabetes. The following postulates have been put forth for the development of PCOS:

1. A defect in the insulin receptor gene has been demonstrated in few patients with PCOS, leading to insulin resistance and hyperinsulinemia. Hyperinsulinemia results in hyperandrogenemia and dyslipidemia.
2. PCOS is said to be due to disordered hypersensitivity of pituitary to the secretion of gonadotropin-releasing hormone (GnRH). This results in increase in secretion of both luteinizing hormone and androgens from ovaries. This causes oligo-anovulation and hyperandrogenism. Androgens are converted to estrogens that further augment pituitary hypersensitivity to GnRH.
3. Obesity is associated with PCOS as it leads to insulin resistance and hyperinsulinemia.
4. Adverse intrauterine environment due to maternal undernutrition or anemia may result in neuroendocrine dysregulation in the fetus leading to insulin resistance and intrauterine growth restriction (IUGR) babies. IUGR babies may develop features of PCOS in adolescence, especially if they have rapid weight gain in infancy and childhood. Rapid weight gain exacerbates the existing hyperinsulinemic metabolic state in these children.

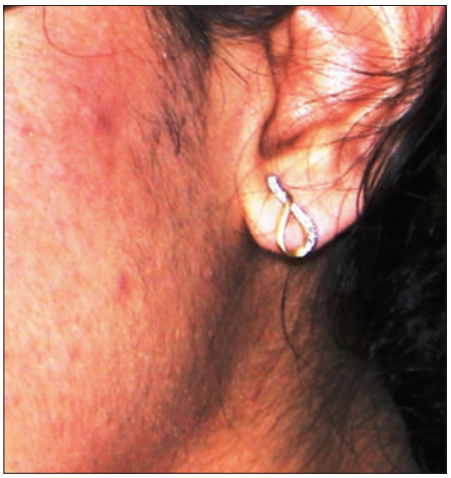

Figure 1: A 14-year-old girl with acne, hirsutism, and acanthosis nigricans suggestive of polycystic ovarian syndrome.

LONG-TERM EFFECTS OF PCOS

PCOS can lead to both morbidity and mortality over the life span, as shown in [Figure 2].[3,4] Health professionals should manage adolescents with signs and symptoms of PCOS early in life. The long-term effects of PCOS are the following:

1. Cardiovascular problems: Hypertension, coronary artery disease, hyperlipidemia, and obstructive sleep apnea syndrome are seen in patients with PCOS.
2. Endocrinal problems: Type 2 diabetes, non-alcoholic fatty liver disease, and metabolic syndrome may develop in adolescence or adulthood. Metabolic syndrome comprises cardiovascular disease risk factors associated with insulin resistance, namely, glucose intolerance, dyslipidemia, hypertension, and central obesity. Hyperandrogenemia in PCOS may contribute to metabolic syndrome independent of obesity. Hence, lean PCOS is also prone to develop metabolic syndrome.
3. Reproductive health problems: Infertility, gestational diabetes, pre-eclamptic toxemia, preterm labor, recurrent miscarriage, and endometrial carcinoma are

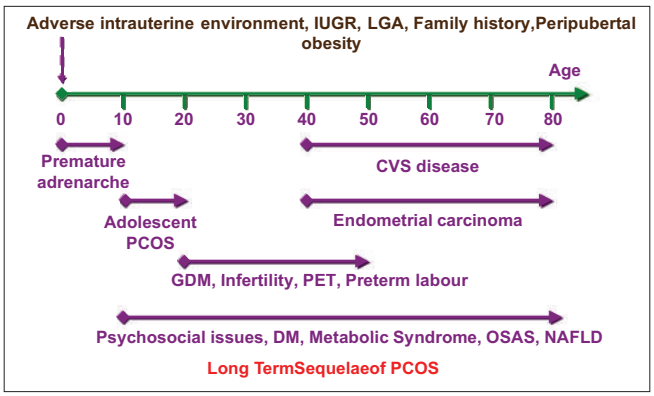

Figure 2: Long-term sequelae of polycystic ovarian syndrome. CVS: Cardiovascular, GDM: Gestational diabetes mellitus, PET: Pre-eclamptic toxemia, DM: Diabetes mellitus, OSAS: Obstructive sleep apnea syndrome, NAFLD: Non-alcoholic fatty liver disease.

said to occur with adult PCOS. PCOS contributes to 30–40% of overall infertility in women. Unopposed estrogenic stimulation in PCOS leads to endometrial carcinoma in adulthood.

4. Psychosocial issues: Body image problems, depression, anxiety, suicidal behavior, eating disorders, disordered eating, and poor self-esteem are associated with PCOS.

Clinical presentation

Menstrual disorders with hirsutism are the most common clinical presentation of PCOS in adolescence.[2-4] Adolescents may present with secondary or primary amenorrhea. Obesity is seen in 50–70% of adolescents with PCOS. They have severe acne that is refractory to topical treatment and have androgenic alopecia in the form of male pattern frontal balding. They usually have body image concerns and may have clinical depression and anxiety. PCOS can also present with primary amenorrhea in adolescence.

The clinician should be sensitive and empathetic during history taking and examination. HEEADSSS psychosocial history should be taken from the adolescent in privacy and with confidentiality. HEEADSSS is an acronym that stands for various domains of an adolescent's life including home, eating, education, activities, drugs, suicide/depression, sexuality, and safety. Dietary intake, level of physical activity, details of media usage, body image concerns, bullying and teasing by peers, difficulty in sleep, snoring, and features of depression and anxiety should be elicited. Eating disorders and disordered eating may coexist with PCOS and should be asked for in particular. Menstrual history should be taken in detail. Family history of similar complaints and a birth history regarding IUGR should also be taken by the clinician.

On examination, height, weight, and body mass index (BMI) are plotted on the Indian Academy of Pediatrics growth charts.[5] It is also important to measure waist circumference (for evaluating central adiposity), sexual maturity rating, and blood pressure.[6] The BMI cutoffs for overweight and obesity are lower in South Asians as they are prone to develop metabolic syndrome at lower values. BMI >25 signifies obesity and between 23 and 25 indicates overweight. Waist circumference varies with age and centile charts are available. At 18 years of age and above, waist circumference of >80 cm indicates central adiposity. Hypertension is often associated with PCOS, obesity, and metabolic syndrome.

Hirsutism is graded using the modified Ferriman–Gallwey scoring system and acne is graded as mild, moderate, or severe. A modified Ferriman–Gallwey score of >4–6, depending on ethnicity is considered significant. These scoring systems assess clinical severity and help in follow-up. They give objective assessment of improvement when the adolescent is on treatment. Acanthosis nigricans, a clinical indicator of insulin resistance, may also be seen, as shown in [Figure 1]. Androgenic alopecia, clitoromegaly, increased muscle mass, and deepening of voice usually indicate an androgen-producing tumor. A mental health assessment for depression, anxiety, eating disorders, and suicidal behavior including ideation and thoughts is also conducted.

Investigations are done to demonstrate biochemical hyperandrogenemia and to rule out other causes of hyperandrogenemia and amenorrhea.[2-4,7] These include calculated free testosterone, calculated total bioavailable testosterone, free androgen index. 17-hydroxyprogesterone (to rule out congenital adrenal hyperplasia), dehydroepiandrosterone (to rule out adrenal tumor), cortisol, thyroid function tests, prolactin, urine pregnancy test, and ultrasound (to rule out adrenal and ovarian tumors) are advised.

It is recommended to use liquid chromatography–mass spectrometry and extraction/chromatography immunoassay for the accurate assessment of total or free testosterone. Enzyme-linked radioimmunoassays for testosterone should not be used preferably as they lack accuracy. High levels of testosterone have not been clearly defined in adolescence and a level above 55 ng/dl may be considered elevated. If the adolescent is on oral contraceptives, it is recommended to stop these drugs for 3 months before a testosterone assessment as these are known to interfere with the biochemical result.

If clinical features of insulin resistance and metabolic syndrome are present, namely, acanthosis nigricans, overweight and hypertension, an oral glucose tolerance test, HBA1c, lipid profile, and liver function tests are mandatory. These are also indicated if there is a family history of PCOS, diabetes mellitus, and an early cardiovascular event at <55 years in a close relative.

Management

Children who were born as IUGR, large for gestational age, and whose mothers have PCOS are known to develop PCOS in adolescence. Those who put on weight rapidly in peripubertal years and with premature adrenarche are at risk. Hence, health professionals should closely follow-up these children with annual health checkups and ensure optimal weight at all ages. They should impart anticipatory guidance regarding balanced nutrition, physical activity, and healthy media usage.

Management of adolescent PCOS is multidisciplinary. Pediatrician, gynecologist, endocrinologist, nutritionist, dermatologist, and psychologists should collaborate for optimizing the case management. Goals of treatment include immediate relief of symptoms and prevention of long-term sequelae.[7]

Therapeutic lifestyle change (TLC) and psychosocial support with culture sensitive, respectful, and empathetic counseling are the cornerstones of therapy. Technique of motivational interviewing should be used by health professionals to encourage adolescents to eat a balanced wholesome diet and to increase physical activity. Intake of equal amount of carbohydrates and protein is encouraged along with food rich in omega 3 fatty acids such as fish, germinated sprouts, and walnuts. Adolescents with obesity and metabolic syndrome should have food with low glycemic index like whole grains and fiber. They should avoid intake of transfats in the form of processed food, bakery products, and fried food. Weight-related stigmatization is to be avoided during counseling. Behavioral modification for weight reduction includes goal setting, self and stimulus control (to avoid intake of high fat salt and sugar diet), mindful and slow eating, and assertive training to deal with negative peer pressure. Under the influence of peers, adolescents are known to binge on high calorie nutrient poor snacks.

Adolescents are counseled regarding benefits of regular moderate-to-severe intensity aerobic exercise for a minimum of 60 min/day and muscle and bone strengthening exercise at least 3 days in a week. Fun activities such as cycling, outdoor group play, tennis, badminton, and swimming are encouraged. Sedentary activities like digital media viewing are limited to 30–60 min/day. Parents are motivated to formulate a family media plan and role model a healthy lifestyle. Weight reduction of even 5% is known to result in spontaneous resumption of menstrual cycles and lower androgen levels.

Life skills such as stress management, relaxation techniques (yoga, meditation, and hobbies) problem solving, coping skills, and critical thinking are taught to adolescents to prevent emotional eating and to deal with body image issues. Depression, anxiety, and eating disorders are managed by cognitive behavior therapy and interpersonal therapy. Moderate-to-severe cases of depression and anxiety may require a psychiatric referral and a prescription of selective serotonin reuptake inhibitors like fluoxetine in a dose of 10–40 mg OD for 9–12 months.

Pharmacotherapy of PCOS includes drugs for the management of metabolic syndrome, Type 2 diabetes mellitus, menstrual irregularities, hirsutism, and acne. Metformin can be used if there is evidence of overweight, metabolic syndrome, Type 2 diabetes mellitus, and insulin resistance. The initial dose is 500 mg OD and can be increased to 1000 mg in daily divided doses. Side effects of metformin are nausea, vomiting, and dyspepsia.

Combination oral contraceptives (COC) containing ethinyl estradiol (at lowest effective dose 20–30 μg) and desogestrel are used for 6–12 cycles to regularize menstrual cycles, to decrease hirsutism, and to prevent the development of endometrial carcinoma. COC can cause thromboembolic phenomena and their use is restricted in adolescents with hyperlipidemia and hypertension. Cyclical progesterone in the form of medroxyprogesterone acetate 10 mg OD is an alternative to COC in adolescents who do not have hirsutism.

Antiandrogens like spironolactone 50–100 mg BD may be used for the management of hirsutism. Minocycline 50 mg OD is used for the treatment of severe acne. It may require therapy with retinoic acid compounds under the supervision of a dermatologist. Cosmetic procedures such as epilation, bleaching, waxing, chemical depilatory creams, electrolysis, laser, and eflornithine hydrochloride cream could also be used for managing hirsutism.

Clomiphene citrate, gonadotropins, laparoscopic surgery, and *in vitro* fertilization may be considered in married adolescents with PCOS and infertility. Bariatric surgery is recommended for morbidly obese adolescents with BMI > 35, with metabolic complications, after they have attained Tanner Stage 5 and have had a poor response to therapeutic lifestyle change and pharmacotherapy for 6–12 months.

Regular follow-up of adolescent PCOS is essential to mitigate immediate health problems and long-term sequelae. Frequent health visits at 1–2 months interval are recommended until menstrual regularity and emotional well-being are attained. Annual health checkups until adulthood are essential. The diagnosis is revisited after 8 years of menarche and a transition of care from the pediatrician to the adult physician is carefully planned.[1] Women with a confirmed diagnosis of PCOS would require regular health checkups and screening for cardiovascular issues, metabolic problems, and endometrial cancer over the entire life span.

CONCLUSION

Oligoanovulation and features suggestive of hyperandrogenemia in adolescence are pointers towards PCOS. It can lead to body image issues, mental disorders and metabolic syndrome in adolescence. Management of PCOS in adolescence is known to reduce its long term complications of cardiovascular disease, infertility and endometrial carcinoma in adulthood. Long term follow up of patients with PCOS is recommended over the entire life span.

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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Review Article

Food allergy: Mechanisms, diagnosis, and management

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ABSTRACT

Food allergy (FA) is a dynamic field. It is not only evolving but also increasing in the prevalence and incidence all over the world. The term "Food allergy" is often misused, not only by patients, their families but also by health professionals. All adverse food reactions are erroneously labeled as "Food allergy." This has to be recognized and avoided to make a proper evaluation, diagnosis and management. Surveys have shown that the prevalence of FA based on public perception runs as high as 60%, whereas the true prevalence is around is around 2–8%. FA is more common in early childhood days (6–8%) compared to adults (1–2%). There are several known and unknown reasons for changing picture of FA across the globe. In the developed world, the peanut sensitivity has doubled in prevalence over the past decade. In the developing world (namely, India, and China), the prevalence of Peanut sensitivity/allergy is much less, although the consumption of Peanuts is much higher. Lately, it has also been observed that early introduction of so called "allergenic foods" to infants and children early in life seems to actually reduce the incidence of allergies developing later in childhood.

Keywords: Food allergy, sensitization, Skin prick test, ImmunoCap, Oral food challenge

Definitions

1. Adverse food reaction: Generic terminology encompassing all untoward reactions to foods
2. FA: A FA occurs when the body's immune system sees a certain food as harmful and reacts by causing symptoms. Foods that cause allergic reactions are allergens. It can be immunologic (IgE) (milk, egg, and nuts) or non-immunologic (non-IgE) mediated reactions (celiac disease)
3. Food intolerance: Metabolic (lactase deficiency)

Food toxicity (food poisoning): Toxins from bacteria, decaying organisms (scombroid fish poisoning).

MECHANISMS OF DEVELOPMENT OF FOOD ALLERGY (FA)

The majority of children do not develop FA. Food allergens are generally weak immunogens. Our gastrointestinal tract by unique mechanisms protects us from developing allergy to multiple food antigens which we ingest daily. Glycocalyx is a sticky lining along the mucosal surface providing the seal between intestinal cells as well as a cementing barrier capable of trapping food particles. This is an efficient barrier system and an essential to maintain the epithelial integrity. In spite of the efficient barrier system, about 2% of ingested food antigens gets absorbed in an immunologically stable form.[1,2]

Oral tolerance

Food antigens are generally weak immunogens. The antigen presenting cells in the GI tract are said to be "non-professional" and are not capable of eliciting a T cell response. The Treg (T regulatory) cells as well as gut flora also play a role in the propagation of oral tolerance. Exclusive breastfeeding also promotes the development of oral tolerance.

Role of gut microbiota

The microbiota inhabiting the normal healthy gut is predominantly Gram negative and shed endotoxin, which through a process activates luminal B cell to preferentially produce IgA and IgG antibodies and thus maintain the integrity of mucosal immunity. On the other hand, disturbance of normal healthy microbiota, that is, dysbiosis, will activate luminal B cells to preferentially produce IgE in place of IgA and IgG and increase susceptibility to allergic diseases.

Early use of broad spectrum antibiotics in 1st year of life and cesarean section will disturb normal healthy microbiota development in gut resulting in dysbiosis and predilection of allergies.

IGE MEDIATED FA

Sensitization to food allergen can occur in two different ways:

The term allergic sensitization describes the first induction of an allergic immune response on allergen encounter. Two routes of allergic sensitization are well established.

Class 1 allergens (e.g., milk, egg, or peanut) are oral allergens that cause sensitization through the gastrointestinal tract.

Class 2 food allergens are mainly allergens in air (e.g., major birch pollen allergen Bet v 1) that causes sensitization through the respiratory tract. These allergens can have cross-reactivity with similar food allergens.

In genetically predisposed individuals, due to the defective epithelial barrier or weak oral tolerance, the food antigens leak through the gut to facilitate sensitization. On re-exposure of the food antigens, specific IgE antibodies residing on mast cells and basophils in the gut bind to the ingested food allergen. This leads to the release of several mediators and cytokines responsible for the clinical cascade of an allergic reaction.

Non IgE mediated FA

A number of non-IgE mediated food hypersensitivity disorders have also been identified. The exact mechanism involved in such disorders is still a matter of debate in certain situations. Non-IgE mediated FA encompasses a wide range of disorders affecting many systems.

Gastrointestinal tract

- Food protein induced enterocolitis syndrome (FPIES)
- Food protein-induced allergic proctocolitis
- Food protein-induced enteropathy
- Celiac disease.

Skin

It contacts dermatitis to foods.

COMBINED IGE-MEDIATED AND T CELL-MEDIATED GASTROINTESTINAL DISORDERS

Eosinophilic esophagitis

Diagnostic tests in FA

In an immunoglobulin E (IgE) mediated reaction; there are the following components to be considered for diagnosis.

1. Thorough clinical history for possible identification of causative allergens
2. Demonstration of allergen specific IgE by allergen skin prick testing (SPT) or *in vitro* blood tests (specific IgE immunoassay)
3. To determine whether exposure to the causative allergens will result in symptoms, either by history or challenge, if needed.

INVESTIGATIONS IN FA

Skin tests and *in vitro* specific IgE tests share many common properties. They show that the patient harbors IgE antibodies directed against the food allergen, which is the same as saying that he or she is sensitized.

Therefore, specific IgE testing helps to confirm a diagnosis of allergy to a specific food, but is of limited utility if interpreted without or in an inappropriate clinical context.[3]

Skin tests are often preferred to blood testing because skin tests are cheaper (especially when many foods have to be tested), they provide the answer in 20 min and they offer a visual cue to the patient.

Blood specific IgE is indicated only in these instances.

a. The patient does not have healthy skin for testing (e.g., severe atopic dermatitis or dermographism)
b. The patient's reaction was anaphylactic and the doctor is not willing to risk even a skin test; and
c. The patient cannot stop using antihistamines.

Skin tests in FA

Studies on aeroallergens showed that skin tests are generally more sensitive than *in vitro* specific IgE test[4,5] though a study on cow's milk and egg allergy in children showed good correlation between the two.[6]

To reduce the likelihood of a false negative result, patients have to stop using antihistamines before skin testing. The length of time of withdrawal depends on the nature of the antihistamine. For example, long-acting antihistamines such as loratadine and cetirizine should be avoided for 10 days and short-acting ones such as chlorpheniramine and diphenhydramine for 3 days before the test.[7]

Skin test reagents are commercially available for many common food allergens. Another advantage of skin test is its flexibility. The test material is placed on the skin (usually the volar aspect of the forearm or the back in children) and the skin is pricked through the reagent, just penetrating the dermis, and without drawing blood. The reading of the SPT is done in 15–20 min. Positive histamine and negative controls are always included in the test.

In the skin test, the wheal (swelling) and flare (redness) responses in 15 or 20 min are recorded. The positive control must show a strong response and the negative control minimal or no response for proper interpretation. A wheal of >3 mm, equal to or above the positive control is considered as a positive test [Figure 1].[8,9,10]

Measurement of allergen-specific IgE

Radioallergosorbent test was the usual way of performing this test, but enzyme methods (e.g., fluorescent enzyme immunoassay, and FEIA) are more commonly used now.[8]

It is better to wait for 4–6 weeks to elapse after an IgE-mediated hypersensitivity reaction before assaying the specific IgE concentration because the IgE is consumed during the reaction, and therefore, may be falsely negative.

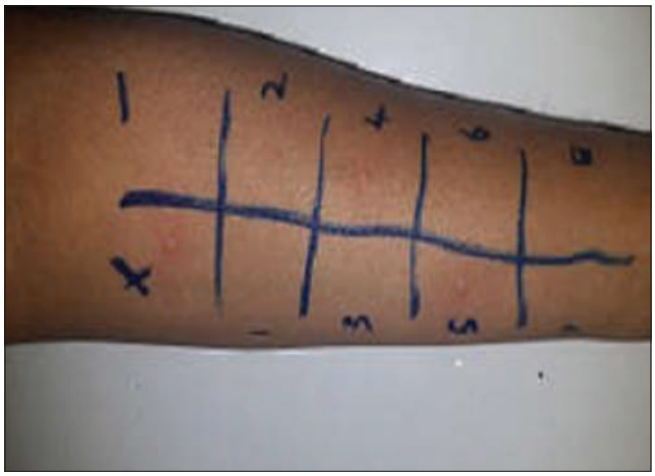

Figure 1: Allergy skin prick test for foods with histamine and saline controls.

The concentration of specific IgE is reported in terms of classes, even though modern equipment is capable of providing a precise quantitative result.

ORAL FOOD CHALLENGES (OFC)

OFC are performed by feeding the patient the suspected food under physician observation.

There are several situations in which physician –supervised OFC are required for diagnosis of food allergic disease.

1. In general when several foods are under consideration as a cause of symptoms, tests for specific IgE are positive, the positive predictive value of a positive ST for food is only 50%. Hence, it might be necessary to conduct an oral challenge to decide regarding reintroduction of food item
2. If tests for specific IgE false positive, challenges may be only way of diagnosis
3. Oral challenges are also an integral part of following patients likely to lose their clinical reactivity to the food in question. Since skin test may remain positive for years following the achievement of clinical tolerance to a particular food, OFC are often the only means to determine whether the allergy has been "outgrown"
4. OFC are strictly to be done in a setting equipped to deal with severe allergic reactions as these reactions can be expected and should be appropriately dealt with.

Diagnosis of Non-IgE mediated food allergies

- Diagnosis made by allergist or gastroenterologist

It is easily misdiagnosed: Because it is not your typical FA as symptoms are not immediate and do not show up on standard allergy tests as described above or in biopsies, unless IgE also present as in atypical FPIES.

Blood tests during acute reaction mimic the body's response to infection.

Atopy patch testing is not validated but may be helpful in delayed reactions.

It may present acutely or chronic and mimic other disorders of infancy, additional symptoms secondary to reactions may be present (making it more difficult to pinpoint diagnosis).

OFC is the most definitive test, however, not often needed initially if the doctor has excluded other diagnosis and the medical history is consistent with the diagnosis.

Present research in FA

As the focus has been shifted to the prevention of infections in keeping the environment more sterile and minimalist

interaction between human, animals, and microbiota, it has seen the surge of allergic diseases since late 1990s. There has been an increased emergence of food allergies in the past two decades with awareness of common foods causing FA. At present, the research focus is on treatment and any measures which can help in prevention of food allergies.

Even though few studies, initially have shown some promising results of bacterial products in preventing atopic dermatitis and augmentation of sustained oral tolerance in food oral immunotherapy (OIT),[11] not all studies have been promising. At present, there are no recommendations for use of microbial products in the treatment or prevention of FA by the world allergy organizations.

The earlier recommendations of highly allergenic food avoidance in the west were withdrawn as studies failed to show beneficial effects of the same.

The learning early about peanut allergy (LEAP) study[12] from United Kingdom was a very interesting study, which involved high risk babies (with egg allergy, eczema, or both) who were randomized to two groups of peanut consumption and peanut avoidance. They reported that in the peanut consumption group, at risk of developing peanut allergy, showed a marked reduction of odds of 70–80% of peanut allergy. This has led to re-work on guidelines endorsing age appropriate weaning foods and no role of avoidance of highly "allergenic" foods, which are essential for nutrition of a growing child.

A lot of research has been ongoing with promising results, to impart of sustained immune tolerance to allergenic foods by consumption of these foods in desensitization to foods by OIT or sublingual immunotherapy. Tolerance implies that the food can be ingested without the appearance of allergic symptoms despite periods of withdrawal.

There has been promising evidence on adjuvant of omalizumab with multiple food allergen OIT and has been shown to reduced time (about 67 weeks) taken for developing tolerance to these foods in Phase 1 of these trials, saving them about 67 weeks' worth of time if they had undergone desensitization to individual foods.[13] There are some outstanding issues with OIT. Uncontrolled nature of most of the trials, different parameters included in the methods and heterogeneity in protocols is to name a few. However, the time may be ripe for the practice of OIT in clinical practice in the coming years.

In conclusion, as we are encountering increased prevalence of FA as a part of Allergic March, time has come to build on available knowledge and to set up new studies which can provide us more armor in the near future.

Quick pointers

1. In the clinical scenario, the emphasis is still on a good clinical history and examination, demonstration of IgE-mediated reaction with correlated ingested foods either with SPT or *in vitro* testing, patient education about avoidance of causative foods and treatment of allergic reactions
2. The attending medical practitioner must take into account the context in which he or she practices and the patient's condition when choosing between skin testing and *in vitro* specific IgE testing
3. SPT are safe, fast, inexpensive (as compared to serum specific IgE) and easy to perform. It can be safely performed even in the infancy with minimal risk. It is better performed by personnel trained with the technique. It has moderate to good correlation (with sensitivity of 50–60% and specificity of 80–90%) with the serum specific IgE in food allergies. This is reassuring for patients with contraindications/access to either test as the results will likely match[14]
4. The practitioner should not order a large number of specific IgE tests to screen for allergy when the diagnosis of IgE-mediated FA has not been established
5. The common foods causing food allergies include milk, egg, wheat, fish, and peanut among others. Therefore, usually SPT to about 8–10 foods will be able to diagnose majority of food allergies
6. All the tests will have to be interpreted in the context of clinical history, which should drive the advice on avoidance of particular foods, rather than blanket avoidance of foods. Misconceptions about FA exists because of correlation of a positive test result to a particular food (either by SPT or serum specific IgE) to having a FA[15]
7. OFC are the gold standard for the confirmation of a FA. In a majority of cases, combination of accurate history and allergy testing (either by SPT or serum specific IgE) can accurately diagnose or exclude FA. OFC may be needed only when the history or test results or both are inconclusive[15]
8. Food allergies can cause anaphylaxis, if not recognized and treated, can be life-threatening. Use of intramuscular epinephrine (0.3 mg for adults and children above 30 kg, 0.15 mg for children <30 kg, and with repeat dose if needed) should not be delayed in such instances, along with supportive management. Subsequent testing for food allergens must be deferred until 4–6 weeks
9. Even though there are promising results in the role of probiotics in prevention or augmenting the desensitization or OIT process from few clinical trials, there are yet currently no recommendations for its use in clinical practice by World Allergy Associations
10. In view of results of LEAP study and similar ones, there is more emphasis on introduction of age appropriate weaning foods in the west. It can be attributed to the same fact that FA is less prevalent in the Indian scenario

as age appropriate weaning foods are traditionally followed in Indian households

11. There is no role for testing serum total IgE/absolute eosinophil count/total IgG4 levels in the diagnosis of food allergies as it does not give any useful information regarding the diagnosis, prognosis, or management
12. Children with moderate to severe atopic dermatitis may benefit from investigations to assess for FA. The investigations must be interpreted in context and confirmed with food challenges and, if necessary, food avoidance. In most situations, these tests should be carried out by specialists experienced in treating food allergies
13. Specific foods such as banana, citrus foods are incriminated in aggravation of concomitant respiratory conditions such as asthma or allergic rhinitis. It may be because of increase in naturally occurring histamine in these foods, which may act as triggering of an acute exacerbation.

It may also be related to oral allergy syndrome, which occurs in patients with allergic rhinitis with pollen sensitization. In these patients, eating of foods which are cross reactive to certain pollens, they cause tingling sensation or itching in the oral cavity but do not cause any systemic symptoms.

Hence, advice for unnecessary avoidance of foods must be given with discretion to parents, bearing in mind, that this can cause micronutrient deficiency in children, if done without proper scientific reason.

Declaration of patient consent

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

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Conflicts of interest

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Karnataka Pediatric Journal

Original Article

Perinatal outcomes of hypertensive disorders of pregnancy

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ABSTRACT

Objectives: Hypertensive disorders of pregnancy (HDP) are multisystem diseases, which include chronic (pre-existing) hypertension, gestational hypertension, pre-eclampsia, eclampsia, and pre-eclampsia superimposed on chronic hypertension. These disorders may complicate 5%–10% of all pregnancies and are leading causes of maternal and perinatal mortality and morbidity worldwide. This study was done to assess the incidence of HDP and perinatal outcomes in comparison to normal pregnancy. The objectives of this study were to assess the incidence of HDP and its correlation with perinatal outcome.

Materials and Methods: Eighty patients were enrolled for the study, Group A (cases) – 40 patients of HDP and Group B (controls) – 40 normotensive controls, these 40 normotensive controls were properly matched with Group A with respect to age and gestational age. The collected data were analyzed with IBM SPSS statistics software 23.0 Version XVII.

Results: In Group A, 45% were gestational hypertensive patients, 35% were pre-eclamptic patients, 12.5% eclampsia, and 7.5% chronic hypertension. Perinatal morbidity and mortality were increased in HDP when compared with age and gestational age-matched controls. Perinatal mortality was seen in 10% in Group A. In Group B(controls) there were no perinatal mortalities.

Conclusion: The study demonstrated that high parity, low gestational age, lack of antenatal care, having eclampsia, pre-delivery onset of HDP, vaginal delivery, low fetal birth weight, and maternal death were independent predictors of perinatal mortality. The majority of perinatal mortality predictors were also predictors of stillbirths. The strong association of perinatal mortality with eclampsia (a late complication of HDP in the majority) and lack of antenatal care is an indirect evidence for the delay in the utilization of obstetric services.

Keywords: Hypertensive disorders of pregnancy, Perinatal outcome, Birth weight, Apgar

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are the most significant problem in obstetrics. The incidence of pre-eclampsia in hospital practice in India varies from 5% to 15% and that of eclampsia about 1.5%.[1] The incidence of HDP varies in the range of 1–35%.[2] They represent one of the most common problems of pregnancy and lead to increased maternal and perinatal morbidity and mortality. Pre-eclampsia is a multisystem and multifactorial disease and causes cellular death. The objectives of this study were to assess the incidence of HDP and its correlation with perinatal outcome.

Definitions

Gestational hypertension

Blood pressure of more than 140/90 mmHg after 20 weeks in previously normotensive women and hypertension resolves by 12 weeks postpartum.

Pre-eclampsia

Hypertension with proteinuria (≥300 mg/day or persistent dipstick 1+ or urine protein:creatinine ratio ≥0.3) or thrombocytopenia (platelet <100,000/μL), renal insufficiency (creatinine >1.1 mg/dl), liver involvement (serum transaminase levels twice normal), cerebral symptoms (headache, visual disturbances, convulsion), and pulmonary edema.

Chronic hypertension

Blood pressure more than 140/90 mmHg before pregnancy or before 20 weeks gestation or both.

Eclampsia

In women with pre-eclampsia, a convulsion that cannot be attributed to another cause is termed as eclampsia.

MATERIALS AND METHODS

Study was conducted in the Department of Pediatrics in Kempegowda Institute of Medical Sciences, Bangalore, for a period of 18 months. The study comprised 80 pregnant women. Forty patients with HDP (Group A) were included for the study, and the results were compared with 40 normotensive patients (Group B). It was purposive sampling.

Inclusion criteria

Forty pregnant women diagnosed with HDP admitted under Obstetrics and Gynecology department in Kempegowda Institute of Medical Sciences (Group A). Results in Group A were compared with 40 normotensive patients and they were selected according to the age of the patient and gestational age of the cases at the time of delivery for proper matching.

Exclusion criteria

In Group A and Group B, patients with medical comorbidities such as diabetes mellitus, liver disorder, renal disease, and cardiovascular disease were excluded from the study.

METHODOLOGY

After taking, informed written consent from all the patients' demographic features such as age, gestation, and parity were recorder on structured data collection sheet. A detailed medical history of all participants was taken to ensure that they fulfill the inclusion criteria for the study. This was followed by a thorough physical examination of every case and control. Blood pressure of all participants was measured using manual mercury sphygmomanometer twice for each patient at an interval of 15–20 min and then after 2 h of rest, before labeling them as normotensive or with hypertensive disorder of pregnancy.

Statistical data analysis

The collected data were analyzed with IBM SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables. To find the significant difference between the bivariate samples in independent groups, the Unpaired sample *t*-test was used. To find the significance in categorical data, Chi-square test was used similarly if the expected cell frequency is <5 in 2×2 tables; then, the Fisher's exact was used. In all the above statistical tools, the probability value 0.05 is considered as significant level.

RESULTS

A total of 80 cases were studied of which, Group A (cases): 40 patients with hypertensive disorder of pregnancy and Group B (controls): 40 normotensive pregnant women.

In our study group, the majority of the patients belong to 21–25 years age group (age was matched with Group A and Group B for proper matching). The youngest being 18 years and the oldest is 37 years [Table 1].

In Group A (cases), the majority were primigravidas constituting 52.5 %. In Group B (controls), the majority were multigravidas constituting 67.5% [Table 2].

Controls were selected according to the gestational age of cases for proper matching. Majority of the patients were between the gestational age of 37 and 39+6 weeks gestation in both Group A and Group B [Table 3].

Majority of the cases were diagnosed with gestational hypertension followed by pre-eclampsia and 5 were cases of eclampsia. Among 14 pre-eclampsia cases, 5 were cases of severe pre-eclampsia [Table 4].

In Group A (cases), among five patients of eclampsia 3 had intrauterine death, other two babies were shifted to neonatal intensive care unit (NICU), of which one baby died on day 6 (neonatal death) due to preterm complication. In Group A (cases), among five patients of eclampsia three had intrauterine death, other two babies were shifted to NICU, of which one baby died on day 6 (neonatal death) due to preterm complication [Table 5].

Indications of elective lower segment cesarean section (LSCS) among cases and controls were previous LSCS not willing for trial of labor after previous cesarean, previous 2 LSCS, malpresentation, cephalopelvic disproportion, etc. In Group A (cases), maximum percentage was seen in emergency LSCS. In Group B (controls), maximum percentage of patients delivered vaginally [Table 6].

In Group A (cases), only seven babies were more than 3 kg, whereas, in Group B (controls), 13 babies were more than 3 kg. In Group B (controls), none of the babies were <1 kg, whereas in Group A (cases) 3 babies were <1 kg [Table 7].

In Group A, among five cases of eclampsia, three had intrauterine fetal demise. In Group B, only two babies had APGAR of <7/10, whereas, in Group A, there were nine babies of APGAR <7/10. All these APGAR represent 1 min APGAR score [Table 8].

In Group A, there were three intrauterine fetal demises; hence, among 37 babies, 24 babies were admitted in NICU. NICU admissions were maximum (64.9%) in Group A, whereas, in Group B, it was only 25% [Table 9].

DISCUSSION

There are numerous pathophysiological abnormalities in HDP. These changes occur in large extent and are translated into a full clinical presentation of pre-eclampsia, during late pregnancy. In this study, controls were selected after proper matching with the cases with respect to the age of the patient and gestational age at the time of delivery. In Group A and Group B, maximum percentage of patients were in the age group of 21–25 years, with the mean age of 25. According to Hazari *et al.*, mean age among cases were 23 and among controls were 25.[3] In Group A, primigravidas were more compared to multigravidas, constituting 52.5% and 47.5%, respectively, which are consistent with various other studies. Primigravida is a proven risk factor for HDP. According to Sajith, 2014, the highest incidence of hypertension was occurred in primigravida patients (53.8%).[4] Hansen reported a two- to three-fold increase in the incidence in primigravida, and this was supported by Chesley.[5] Sibai and his association recently reconfirmed the high risk of developing of pregnancy induced hypertension in primigravidas.[6-8] Most common hypertensive disorder of pregnancy found in this study was gestational hypertension followed by pre-eclampsia, which is consistent with FOGSI which states that approximately two-third of HDP are due to gestational hypertension and preeclampsia and one-third are due to chronic hypertension. The total number of intrauterine deaths in the study were 3 (7.5 %) due to

Table 1: Distribution of Group A and Group B according to age.

Age (years)	Group A (Cases)	Group B (Controls)
18–20	8 (20.0%)	3 (7.5%)
21–25	16 (40.0%)	21 (52.5%)
26–30	11 (27.5%)	13 (32.5%)
Above 30	5 (12.5%)	3 (7.5%)

Table 2: Distribution of Group A and Group B according to gravidity.

Gravida	Group A (Cases)	Group B (Controls)
Multi	19 (47.5%)	27 (67.5%)
Primi	21 (52.5%)	13 (32.5%)

Table 3: Distribution of Group A and Group B according to gestational age.

Gestational age (weeks)	Group A (Cases)	Group B (Controls)
≤33+6	10 (25%)	8 (20%)
34–36+6	13 (32.5%)	10 (25%)
37–39+6	14 (35%)	18 (45%)
≥40	3 (7.5%)	4 (10%)

Table 4: Distribution of cases according to various types of hypertensive disorders of pregnancy.

Group A – Cases (*n*=40)	Frequency	Percentage
Gestational hypertension	18	45
Preeclampsia	14	35
Chronic hypertension	3	7.5
Eclampsia	5	12.5
Total	40	100

Table 5: Comparison of Group A and Group B according to perinatal outcome.

Perinatal outcome	Group A (Cases)	Group B (controls)
Intrauterine growth restriction-preterm	13 (32.5%)	2 (5%)
Intrauterine growth restriction-term	6 (15%)	0
Intrauterine fetal death	3 (7.5%)	0
Neonatal death	1 (2.5%)	0

Table 6: Comparison of Group A and Group B according to mode of delivery.

Mode of delivery	Group A (Cases)	Group B (Controls)
Emergency lower segment cesarean section	19 (47.5%)	11 (27.5%)
Elective lower segment cesarean section	9 (22.5%)	10 (25%)
Vaginal delivery	12 (30.0%)	19 (47.5%)

Table 7: Comparison of birth weight among Group A and Group B.

Birth weight	Group A (Cases)	Group B (Controls)
≤999 g	3 (7.5%)	0%
1000–1999 g	13 (32.5%)	7 (17.5%)
2000–2999 g	17 (42.5%)	20 (50%)
≥3000 g	7 (17.5%)	13 (32.5%)

Table 8: Comparison of Apgar score among Group A and Group B.

Apgar	Group A (cases)	Group B (controls)
7–10	31 (77.5%)	38 (95%)
4–6	6 (15%)	2 (5%)
0–3	3 (7.5%)	0
Total	40	40

Table 9: Comparison of neonatal intensive care unit admission among Group A and Group B.

Neonatal intensive care unit admission	Group A (cases)	Group B (controls)
No	13 (35.1%)	30 (75%)
Yes	24 (64.9%)	10 (25%)

eclampsia. One case of neonatal death on day 6 of life was due to preterm complications. Perinatal mortality in my study was 10%. The mean birth weight of babies in Group A (cases) was 2.21 and standard deviation of 0.87; the mean birth weight of babies in Group B (controls) was 3.01 and standard deviation of 0.43. The magnitude of fetal growth restriction is more in Group A (cases) than Group B. In this study, in Group A (cases), 12 delivered vaginally (30 %) and 28 by cesarean section (70%). In Group B (controls), 19 delivered vaginally (47.5%) and 21 by cesarean section (52.5%). In the study by M.R. Dutta, Luna Pant (2002), 45% were vaginal deliveries, and cesarean section rate was 62 %. Iqbal *et al.* reported an incidence of cesarean as 43% and vaginal as 57 %. In Group A (cases), 55% were preterm deliveries and remaining were term. An observational study on maternal and neonatal outcome in Thrissur Medical college, conducted in 2017 by Kennady G et al. showed 52.4% preterm.[9] In Group A, only seven babies were more than 3 kg, whereas, in Group B, 13 babies were more than 3 kg. In Group B, none of the babies were <1 kg, whereas, in Group A, there were three babies. In Group A, there were 19 fetal growth restriction babies, whereas, in group B, there were only two cases of fetal growth restriction suggesting that IUGR is a common finding in HDP as seen by Odegard *et al.*[10] In Group A, among five cases of eclampsia, three had intrauterine fetal demise. In Group B, only two babies had APGAR of <7/10, whereas, in Group A, there were nine babies of APGAR <7/10. Limitations of our study – the sample size was small (as patients in Group A [cases] were selected only with HDP and patients with other comorbidities like diabetes, liver disorder, renal disease and cardiovascular disorders were excluded from the study), we did not correlate the levels of the parameter in different classification of HDP and its complications.

CONCLUSION

HDP are common in India. The basic management objectives included obstetric management, adequate fetal surveillance, antihypertensive management, anticonvulsant therapy, safe analgesia, anesthetic management of labor, and anesthesia for delivery. ISSHP recommends that women with established strong clinical risk factors for preeclampsia be treated, ideally before 16 weeks but definitely before 20 weeks with low-dose aspirin (75–162 mg/d as studied in randomized controlled trials). In normal pregnancy, there is decreased blood pressure response to pressor substances, but in pre-eclampsia, there is marked response to vasopressin, norepinephrine, and angiotensin. This response of arterial system leads to generalized vasoconstriction and hypertension in pre-eclampsia. These alterations secondarily lead to many pathophysiological changes which adversely affect maternal and fetal wellbeing. Such cases need special attention with early detection and referral to higher center with better facilities of NICU set up to reduce the complications and mortality. Hypertensive disorders remain among the most significant and intriguing unsolved problems in obstetrics. In further studies, it is critical to find early diagnostic markers which are also cost effective, markers which help us to know the prognosis, effective interventions, and preventions of HDP which are particularly important to reduce maternal and perinatal complications and ensure both pregnant women and neonates to be healthy and safe.

In Group A and Group B, maximum percentages of patients were in the age group of 21–25 years, with the mean age of 25. In Group A, primigravidas were more compared to multigravidas, constituting 52.5% and 47.5%, respectively, whereas, in Group B, multigravidas were more compared to primigravidas constituting 67.5% and 32.5%, respectively. Most common hypertensive disorder of pregnancy found in this study was gestational hypertension followed by pre-eclampsia. The total number of intrauterine deaths in the study were 3 (7.5%) due to eclampsia. One case of neonatal death on day 6 of life due to preterm complication. Perinatal mortality in my study was 10%. The mean birth weight of babies in Group A (cases) was 2.21 and standard deviation of 0.87; the mean birth weight of babies in Group B (controls) was 3.01 and standard deviation of 0.43 In this study, in Group A (cases), 12 delivered vaginally (30%) and 28 by cesarean section (70%). In Group B (controls), 19 delivered vaginally (47.5%) and 21 by cesarean section (52.5%). In Group A, only seven babies were more than 3 kg, whereas, in

Group B, 13 babies were more than 3 kg. In Group B, none of the babies were <1 kg, whereas, in Group A, there were three babies. In Group A, there were 19 fetal growth restriction babies, whereas in Group, B there were only two cases of fetal growth restriction. In Group B, only two babies had APGAR of <7/10, whereas, in Group A, there were nine babies of APGAR <7/10.

Declaration of patient consent

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Parents' experience of receiving their child's diagnosis of Down's syndrome

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ABSTRACT

Objectives: The objectives of the study were to study the parents' satisfaction with the experience of receiving the diagnosis of Down's syndrome (DS) for their child.

Materials and Methods: Children studying in special schools in the city with DS were identified and a retrospective study of their parents' experience on receiving their child's diagnosis was done using a semi-structured, questionnaire, developed, and validated by us.

Results: Forty-two parents participated. In 7 (16.6%), diagnosis was made in the neonatal period, in 15 (35.7%) between 1 month and 1 year, and in 20 (47.6%) after the 1st year of life. Forty (95.2%) had been given printed information, 32 (76.2%) were provided with contacts numbers of resource centers. Thirty-eight (90.5%) were referred to support groups. Only 9 (21.4%) were provided a timetable of care. Twenty (47.6%) felt that all the positive aspects had been clarified, 15 (35%) felt that all the negative aspects were completely explained, and 29 (69%) felt that the doctor had shown compassion. Overall satisfaction 9.5% were very satisfied with the experience, 45.2% were quite satisfied,11.9% were neutral, 19.1% were quite dissatisfied, and 14.3% were very dissatisfied. The factors significantly associated with satisfaction included having a time table of care, having both positive and negative aspects completely explained and the health-care professional showing compassion at the time of breaking the diagnosis.

Conclusion: Only 54.8% of parents of children with DS were satisfied with the way the diagnosis of their child's condition was broken to them. Efforts to include the factors associated with satisfaction and avoidance of factors causing dissatisfaction will help improve the experience of these parents.

Keywords: Down syndrome, Parents experience, Satisfaction

INTRODUCTION

Down's syndrome (DS) has an overall incidence of 1–1.4/1000 live births in India.[1] This is higher compared to other countries offering prenatal diagnosis for DS. Receiving a diagnosis of DS in their child is a memorable experience for an individual and his or her family.[2] Although much is talked about conveying difficult news by medical professionals, there is very little information on parentse the experience of these parents

Objectives

The objectives of the study were to study the parents' experience of receiving the diagnosis of DS for their child.

MATERIALS AND METHODS

Children 1 month–18 years old studying in special schools in the city with confirmed a diagnosis of DS were identified. A retrospective study was done in May–June 2016 of their parents' experiences on receiving their child's diagnosis of DS. The parents who gave written informed consent and remembered the time they received the news well were included for a face to face interview. Approval for the study was obtained from the Institutional Ethics Committee.

A semi-structured questionnaire in English developed and validated by us was used. The face validity of the questionnaire was established by first having it reviewed by five senior pediatricians familiar with the topic and then an expert biostatistician on question construction. We then ran a pilot test on a subset of survey participants (six parents) to remove the confusing or weak questions.

The parents were interviewed in the language comfortable for them using the questionnaire which consisted of prompts to explore the participants' experience. The responses were noted down simultaneously. The interview was not recorded. Satisfaction was graded on a 5-point Likert scale as very satisfied (5), quite satisfied (4), neither (3), quite dissatisfied (2), and very dissatisfied (1). The Likert scale was employed as it has been most recommended by the researchers that it would reduce the frustration level of patient respondents and increase response rate and response quality.

The collected responses were then entered into a spreadsheet and coded. Descriptive statistics were presented as numbers and percentages. A Chi-squared test was used for comparison between the three groups. $P < 0.05$ was considered statistically significant. For statistical analysis, "Minitab Statistical Software," Version 15 was used.

RESULTS

Overall, 57 parents from three special schools in Chennai were approached, of which 15 either were unwilling to take part or were unable to recall the specific events at the time of diagnosis. Only 42 participated, 40 (95.2%) were mother and 2 (4.8%) were father.

The mean age of the children was 8.5 years. Twenty-three (54.8%) children were boys and 19 (45.2%) were girls. The oldest among the surveyed was 18 years old and the youngest was 6 months old. Thirty-seven (88.1%) mothers had undergone antenatal ultrasound scan which was reported to be normal. In the other five, some abnormal finding was noted and further investigations had been suggested to the parents which they had refused. Twenty-six (61.9%) mothers were above the age of 35 at the time of conception while 30 (71.4%) fathers were above the age of 35. Twelve (28.6%) had a consanguineous marriage. Twenty-five (59.5%) had extended family support.

At the time of disclosing the diagnosis, in 35 (83.3%) of the cases, both the parents were present and out of them, in 7 (16.7%), extended family members were also present. In 7 (16.6%) children, diagnosis was made in the neonatal period, in 15 (35.7%) between 1 month and 1 year and in 20 (47.6%) after the 1st year of life. Thirty-five (83.3%) of them had been given the diagnosis by a pediatrician and 7 (16.67%) were given by others. In 35 (83.3%), it was the parents themselves who first noted atypical development with their child. In 21 (50%) babies, the developmental delay was noticed before the year of age 1 and in 21 (50%) it was after 1 year.

Forty out of the 42 (95.2%) parents had not heard the term DS earlier. Forty (95.2%) had been given printed information after the diagnosis was disclosed. Thirty-two (76.2%) were provided with contact numbers of resource centers. Thirty-eight (90.5%) were referred to support groups.

Ten (23.8%) were referred to an early intervention program before the 1st year of life. Twelve (28.6%) of the children began therapy between 1 month and 3 years and 20 (47.6%) beyond 3 years. Only 9 (21.4%) were provided a timetable of care. Twenty-nine (72.5%) felt that all the positive aspects had been explained, 15 (37.5%) felt that all the negative aspects were completely explained, and 29 (72.5%) felt that the doctor had shown compassion when explaining the diagnosis.

Overall, 4 (9.5%) parents were very satisfied with the experience, 19 (45.2%) were quite satisfied, 5 (11.9%) were neutral, 8 (19.1%) were quite dissatisfied, and 6 (14.3%) were very dissatisfied.

The relationships between the variables studies and parents satisfaction are depicted in [Table 1].

DISCUSSION

Out of the parents of 42 DS children who were interviewed, only 54.7% were satisfied with the experience of receiving the diagnosis. The variables associated with satisfaction were diagnosis in the neonatal period, both positive and negative aspects being explained, time table of care being given and the health-care provider showing compassion. The variables associated with poor satisfaction were someone other than a pediatrician giving the diagnosis and only one parent being present at the time of giving the diagnosis.

This rate of satisfaction noted was similar to that reported in earlier studies.[1] The parent's ability to recall exactly how they felt when initially told of the child's diagnosis indicates the importance of the method of delivery of diagnosis. Subsequently, parents rely on their own resources and coping strategies, together with formal support in taking care of their child.[3-6]

Table 1: Factors influencing parents' satisfaction.

Variable	Quite/very satisfied (*n*=23) *n* (%)	Quite/very dissatisfied (*n*=14) *n* (%)	Neither (*n*=5) *n* (%)	Total	*P*-value
Age at diagnosis					
Neonatal period	06 (85.7)	0 (0)	01 (14.2)	07	0.03292
1 month–1 year	10 (66.7)	02 (13.3)	03 (20.0)	15	0.06273
>1 year	07 (35.0)	12 (60.0)	01 (04.7)	20	0.06174
Diagnosis given by					
Pediatrician	23 (65.7)	09 (22.9)	03 (08.6)	35	0.07190
Others	0 (0)	05 (71.4)	02 (28.6)	07	0.03678
At the time of receiving the diagnosis					
Both mother and father present	22 (62.9)	09 (25.7)	04 (11.4)	35	0.07023
Only one parent present	1 (14.3)	05 (71.4)	01 (14.3)	07	0.05798
Additional supports					
Printed material	23 (57.5)	12 (30.0)	05 (12.5)	40	0.07342
Support group referral	23 (60.5)	11 (28.9)	04 (10.5)	38	0.06187
Positive aspects explained	16 (80.0)	01 (05.0)	03 (15.0)	20	0.03371
Negative aspects explained	12 (80.0)	01 (06.7)	02 (13.3)	15	0.04251
Time table of care	09 (100.0)	0 (0)	0 (0)	09	0.00187
Health-care professional showed compassion	23 (79.3)	01 (03.4)	05 (17.2)	29	0.04723

According to the Center for Disease Control and Prevention, although the risk is more with increasing maternal age, around 80% of babies with DS are born to women younger than 35 as younger women have more babies than older women. In our study, 61.9% of mothers and 71.4% of the fathers were above the age of 35 at the time of conception. Out of the 42 parents interviewed in our study, 95.2% were the mother of the child while in the previous studies, the participation by fathers has been much greater (38–42%).[7] This difference could be because culturally mother is the primary caregiver for children in our country.

When the diagnosis was made in infancy, satisfaction was significantly higher. However, when the physical characteristics and developmental delay are mild, diagnosis is often delayed. Studies show that parents who do not know the etiology of their child's delayed mental development suffer more emotional stress compared to parents whose child has a diagnosis of DS.[8]

Parents who were given by health professionals other than a pediatrician reported less satisfaction. Ideally, the parents, obstetrician, and pediatrician should meet jointly with the couple to explain DS, especially when the diagnosis is made in early infancy and the anomaly scan has been reported normal.[9]

Most of the parents (95%) had not previously heard the term DS. Other studies have also revealed that most lay persons would not have heard of DS before and would rely on their primary physician for complete details.[9] and parents are more likely to be satisfied when the diagnosis is accompanied by printed information which they can refer to later and when contact numbers of resource persons are shared. In our study, 95.2% had been given printed information after disclosure,76.2% were provided with contacts numbers of other parents of children with DS, and 90.5% were referred to support groups. In a previous study from Pakistan of 19 children with DS, no parent had been given printed information or contact number of support groups,[10] while in Spain, 19.3% received printed material and 15% received contact numbers of other parents with DS children. In our study, only 21.4% were provided a timetable of care and these parents were more satisfied. It would be advisable for health professional to hand out a timetable of care as this significantly affects the satisfaction level in parents with a DS child.

In our study, 47.6% felt that the doctor had explained all the positive aspects of DS but only 35.7% felt that all the negative aspects were covered. This suggests that our health-care professionals should check the understanding of the parents after delivering the news. While it is important that parents understand the associated intellectual deficits, the positive aspects and the talents and abilities of these children also need to be emphasized. In a Spanish study, 74% felt doctors emphasized the positive aspects and 61% felt that negative aspects were clearly discussed.

Most parents (69.0%) felt that the doctor had shown compassion while delivering the news and this was more in the group with good satisfaction. Although the previous studies have also shown that parenttisfactiond the associated intellectual deficits, the positive aspects and the talentsediatrician, most parents can distinguish between their reaction to the diagnosis and the way in which it is delivered.[11,12] In our study, no patient had prenatal diagnosis suggesting that when prenatal diagnosis of DS is made the

family chooses to terminate the pregnancy.

Mothers who receive a prenatal diagnosis of DS and continue with their pregnancies can experience a better birthing process compared with their counterparts who first learn about the diagnosis postnatally. Receiving the diagnosis in advance allows parents the necessary time to reconcile their own emotions and prepare for the child, if they choose to continue with the pregnancy.[13]

There were some limitations in our current study. Most of the participants were mother and hence the difference between the experiences of mother and father could not be analyzed. As it was a retrospective study in which parents were requested to recall events long after the actual diagnosis, there is a likelihood of recall bias. Parents could have forgotten essential information regarding the diagnostic process or information provided but most parents in this study seemed to recall events clearly. This can be attributed to flashbulb memory.[7,13,14]

CONCLUSION

- Only 54.8% of parents of children having DS were satisfied with the way the diagnosis was given to them
- Diagnosis in infancy, getting a timetable of care, having both positive and negative aspects completely explained, and the health-care professional showing compassion at the time of the diagnosis significantly increased the likelihood of parental satisfaction
- The factors that increased the likelihood of dissatisfaction included delay in diagnosis, not having the spouse alongside, and being told the diagnosis by a person other than the pediatrician.

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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Questionnaire

Parents experience on receiving their child diagnosis of Down's syndrome

Information about the child
Child diagnosed with DS
Child sex
Child age
Date of birth
Mode of delivery
Birth weight
Place of birth
Baby's birth order
Child's age when diagnosed
Antenatal care
Ultrasound
NT scan
Any other test done

Information about the parents		
	Father	**Mother**
Parental age at conception		
Consanguinity		

Information about the family
Type of family
Siblings
Family history of DS

Disclosure of diagnosis

1. Who delivered the diagnosis?
   - Pediatrician
   - Others: Neonatologist/obstetrician/family physician.
2. Where any family members present at the time when the diagnosis was delivered to you?

Diagnostic process and support received after disclosure

1. When did you notice atypical development in your child?
2. When was the definitive diagnosis about your child given to you?
3. Did the doctor/health professional explain the positive aspects of having a child with DS?
4. Did the doctor/health professional give a complete account of the negative aspects?
5. Was any printed information or resources provided to you?
6. Were you given contact numbers/ information for those you could contact about DS?
7. Were you referred to any local support groups
8. Were you provided a timetable of care?
9. What was the age of the child when he/she was referred to an early intervention program

Overall experience

Very satisfied	Quite satisfied	Neither	Quite dissatisfied	Very dissatisfied

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Karnataka Pediatric Journal

Case Report

Congenital eyelid imbrication syndrome in a neonate: A rare case

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ABSTRACT

A full-term newborn was examined after lower segmental cesarean section. There were no antenatal complications. Clinically, there was overlapping of upper lids over lower eyelids when the baby was crying, but reduced when the baby was asleep. The upper eyelids became normal within 2 days of delivery without any treatment. We report one such case.

Keywords: Congenial, Eyelid, Imbrication syndrome

INTRODUCTION

Eyelid imbrication syndrome (EIS) is an extremely rare eyelid malposition disorder, in which the eversion of upper eyelids is seen, sometimes associated with floppy eyelid syndrome.[1] In adults, eyelid imbrication is associated with floppy/lax eyelids, which is usually managed surgically.[2] Till date, five cases have been reported. Here, we describe a case of congenital EIS (CEIS) in a normal healthy newborn presenting with overriding of both upper lids on lower while closure and spontaneous eversion while crying.

CASE REPORT

A full-term boy was born after an uneventful cesarean section at 39 weeks of pregnancy to primipara non-consanguineous parents, weighing 3000 g, who was referred for routine checkup. He was the first child of the family. The pregnancy course was normal, no antenatal drugs were used except for iron and calcium supplementation. No family history suggestive of any ocular malformations. There were no dysmorphic facies or neurocutaneous markers in the baby.

Ocular examination of the baby showed elongated upper lids [Figure 1a] and tarsal plates were overlapping the lower lid margins by more than 2 mm. The upper eyelids (left>right) could be everted with minimal effort due its floppiness. The upper eyelids had a tendency for spontaneous eversion on crying [Figure 1b]. The lids could be manually repositioned. The tarsal conjunctiva of both eyelids showed hyperemia. Pediatric ophthalmologist opinion was taken by teleconsultation and advised topical lubricants. After 48 h, when called for review, there was marked improvement in lid position with decreased overriding and no spontaneous eversion.

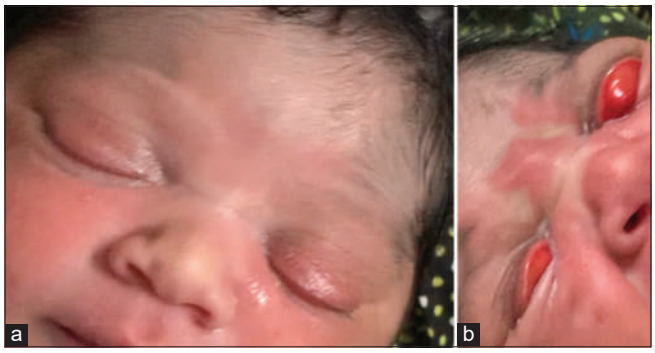

Figure 1: (a) Clinical photograph of a neonate showing overlapping of upper eyelids on lower eyelids on eye closure (left>right). (b) Clinical photograph showing spontaneous eversion of both upper eyelids while crying and tarsal conjunctival hyperemia.

DISCUSSION

The scarce literature of CEIS was due to its spontaneous recovery. This congenital condition is rare in children and is self-limiting and is associated with lax eyelids, whereas acquired condition requires surgical correction. CEIS is frequently associated with congenital floppy eyelid syndrome (CFES).[3,4] There was found to be association with Down syndrome, but this baby did not have those features.[5]

Our case was similar to that of the case reported by Odat and Hina in 2009.[4] He thought that postnatal growth of the bony orbit may contribute to the spontaneous tightening of canthal tendons. However, the other researchers proposed that whole eyelids were bulky and floppy and underwent involutional changes under the influence of unknown effect in the 1st week of life and that resulted in tightening of laxed canthal tendons and normalization of tone and size of the upper eyelids.[6] The classical feature of floppy eyelid syndrome is spontaneous eversion of the eyelid. In CEIS, spontaneous eversion is directly related to the amount of overriding of upper eyelid over lower. This relationship is documented in Odat and Hina.[4] and Chandravanshi *et al*.[6] Congenital lax upper eyelid syndrome can be used instead of CEIS/CFES.

CONCLUSION

CEIS is a rare, transient, self-limiting disorder of unknown cause. The combination of CFES and CEIS should be considered as one of the differential diagnoses of congenital eyelid malposition. A pediatrician should be familiar with CEIS. The floppy eyelid syndrome should be looked for in a case of CEIS.

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 Pediatric Journal

Case Report

Neonatal Group B streptococcal osteomyelitis and suppurative arthritis: A case report

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ABSTRACT

Neonatal sepsis contributes significantly to neonatal morbidity and mortality. Group B streptococcus (GBS) is not a frequent cause of neonatal sepsis in India. Late onset sepsis by GBS presenting as focal infection like osteomyelitis is seen in only 3% of the total GBS sepsis profile in neonates. Here, we report a rare case of neonatal osteomyelitis with septic arthritis caused by GBS at an unusual site, the clavicle and sternoclavicular joint.

Keywords: Neonatal sepsis, Osteomyelitis, Septic arthritis, Group B streptococcus

INTRODUCTION

Neonatal sepsis continues to be a major global public health challenge.[1] Neonatal sepsis can be classified into early-onset sepsis and late-onset sepsis depending on the age of onset of symptoms. Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without bacteremia. It encompass various systemic infections such as septicemia, pneumonia, meningitis, osteomyelitis, arthritis, and urinary tract infections.[2] Gram-negative organism is the most common cause for neonatal sepsis with Klebsiella species being the most common organism as per the data available from India.[3-5]

Group B streptococcus (GBS) is an encapsulated gram positive diplococcus. Maternal colonization in the genital tract is the primary risk factor for GBS infection. Late onset sepsis by GBS manifests as bacteremia without a focus (65%), meningitis (25%), and cellulitis and osteoarthritis (2–3%) each.[6] The incidence of GBS infection was only 0.17 per 1000 live birth over a period of 10 years in a large tertiary care center in South India,[7] highlighting the rarity of GBS as an important neonatal pathogen. Low rate of maternal colonization and high prevalence of protective maternal antibody could be the reason for the low incidence of GBS sepsis. Existing data suggest that at least half of the infants with late onset disease by GBS are born preterm (before 37 weeks). Late onset disease has a lower fatality rate (1%–6 %) than early onset disease.[6]

Osteomyelitis in neonates is not so common. The global incidence of neonatal osteomyelitis is only 1–7 per 1000 NICU admissions.[8,9] Acute osteomyelitis is most commonly caused by *Staphylococcus aureus* and, less often, by GBS species and Gram-negative bacteria such as *Escherichia coli* and *Klebsiella pneumonia*.[10-12] Osteomyelitis due to GBS is common in humerus (56%), femur (24%), tibia and talus (4%), and others (ilium, clavicle, skull, digit, vertebrae, and ribs).[6] Clavicle is the first bone to ossify in human embryo and is the only long bone to ossify

intramembranously. Literature review showed 16 cases of acute clavicle osteomyelitis in children and adolescents (age ranging from 0 to 16 years). Among these 16 cases, *S. aureus* was the most common organism isolated.[13-17]Septic arthritis is the invasion of a joint by an infectious agent resulting in joint inflammation. Global incidence of neonatal septic arthritis is approximately 0.3 per 1000 live births, whereas in India it has been reported as 0.6 per 1000 live births.[18] A study conducted in a tertiary care hospital in West Bengal showed, *K. pneumoniae* was isolated in more cases of neonatal septic arthritis, followed by *S. aureus* and *E. coli*.[19] Septic arthritis caused by GBS is most commonly encountered in hip (56%), knee (38%), and ankle joint (6%), respectively.[6]

CASE REPORT

A 14 days old Term/AGA/Female neonate, born by normal vaginal delivery with no significant antenatal, natal and immediate postnatal history was admitted with complaints of swelling over the right side of the chest [Figure 1]. There was no history of fever. On examination, baby was afebrile, icteric, and hemodynamically stable with a swelling over the medial end of right clavicle. Baby was moving right upper limb, with no cry on manipulation at right shoulder joint. The initial differentials considered were fracture clavicle/abscess/osteomyelitis/Caffey's disease/congenital syphilis.

Investigations revealed a blood leukocyte count of 35,200/mm^3 with 58% neutrophils, 40% lymphocytes, and a platelet count of 799,000/mm^3. CRP was 380 mg/dl. USG chest was suggestive of evolving abscess/hematoma [Figure 2]. On needle aspiration of the swelling around 1 ml of thick pus was recovered which showed many pus cells on Gram stain and subsequently showed growth of Group B beta-hemolytic streptococci (*Streptococcus agalactiae*). CT right sternoclavicular joint confirmed the diagnosis of right sternoclavicular septic arthritis with osteomyelitis of medial end of right clavicle [Figure 3]. Right sternoclavicular joint arthrotomy and osteomyelitis decompression of right clavicle were done. Child was started with Inj Ceftriaxone and oral linezolid. Child was given Inj ceftriaxone for 12 days and linezolid was continued for a total duration of 6 weeks. Child responded to treatment well and was on regular follow-up. Serial counts of CRP showed a declining trend. If resistant, we plan to workup for primary immuno-deficiency especially phagocytic defects.

DISCUSSION

Neonatal osteomyelitis occurs secondary to bacteremia and often insidious in onset. The proliferative vascular blood supply in the developing skeletal system of the neonates makes them prone to develop osteomyelitis. Metaphyseal region of the long bones especially the femur and the tibia is the most common sites involved. Osteomyelitis can also occur secondary to an extension from focal infection or bone trauma.[20] Other risk factors for osteomyelitis in preterm babies include umbilical catheterization and catheterization of other sites, especially the groin vessels. Septic emboli may form on vascular catheters, setting up a relatively high-inoculum bacteremia. Such risk can be reduced by following strict aseptic precautions while placing the lines. Studies have shown that urinary tract infection, periumbilical skin infections, and venous cut-downs for intravenous access also as risk factors for osteomyelitis.[21]

The long bones especially femur and tibia accounts for almost 50% cases of neonatal osteomyelitis, with humerus and the fibula being the next most commonly infected long bones.[21] Once bacterial infection sets in the metaphyseal vessels, inflammatory pathways begin leading to abscess formation. Abscess can rupture through the outside of the bone, forming a periosteal abscess, or through the side of the bone into the joint space, causing septic arthritis.[21]

Although Gram-negative bacilli account for 33% of neonatal sepsis, they only cause about 5% of cases of osteomyelitis. *S. aureus* being the most common organism causing neonatal osteomyelitis,[10] the incidence of methicillin-resistant *S. aureus* is increasing. GBS and coagulase-negative staphylococci rarely cause osteomyelitis. In preterm neonates Gram-negative organisms such as *E. coli*, *K. pneumoniae*, *Enterobacter cloacae*, *Salmonella enteritidis*, and *Citrobacter freundii* can cause osteomyelitis.[21] Although osteomyelitis from fungal infection is rare, the incidence is increasing.[21] Even in babies with disseminated congenital tuberculosis infection, osteomyelitis is rare.

Plain film radiography typically shows swelling of contiguous soft tissues; osteolytic and periosteal lesions, such as bone destruction and periosteal new bone elevations; and pathologic fractures, and typically of the long bones. Ultrasonography may not be specific for neonatal osteomyelitis.[22] Radionuclide bone scans are more sensitive than plain radiography in the early phase of the disease when X-ray changes have not appeared but are not always reliable. Conventional radiography still remains the first imaging modality because it is cheap and easily available. Periosteal and lytic changes are seen usually 10–21 days after onset of symptoms.[23] MRI provides more accurate details regarding the extent of the disease. Aspiration of the affected joint provide diagnostic clues and sometimes for therapeutic purposes.

Appropriate selection of antibiotics and surgical drainage of pus if any plays an important role in treatment of osteomyelitis. Normally, anti-staphylococcal antibiotics such as nafcillin, cefazolin, or vancomycin along with a second- or third-generation cephalosporin (e.g., cefuroxime, and

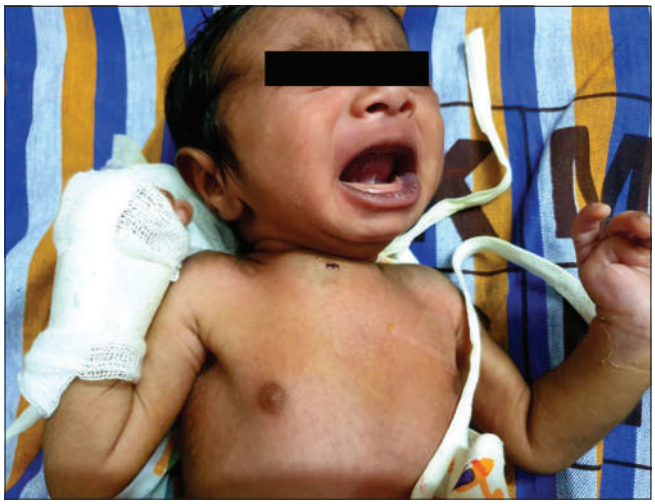

Figure 1: Clinical picture.

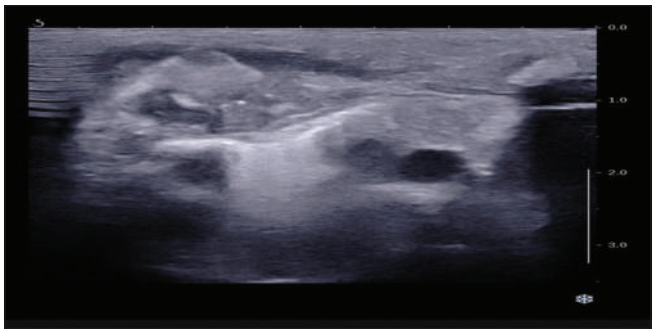

Figure 2: USG chest

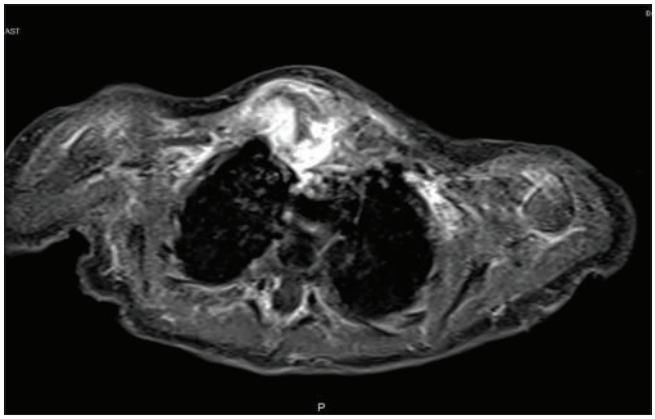

Figure 3: CT sternoclavicular joint

cefotaxime) or an aminoglycoside (e.g., gentamicin, and tobramycin).[25] Antibiotic selection must be personalized to individual clinical factors and culture results. If there is no response to antibiotics, then surgical correction with necrotic debridement should be considered.

The total duration of antibiotics is usually 4–6 weeks preferably by intravenous route.[21] To prevent recurrence appropriate intravenous antibiotics should be given for at least 4 weeks, after resolution of the infection has been documented (e.g., negative culture results).[24] Jagodzinski *et al.* suggest a shortened course of treatment, in which patients with osteomyelitis are converted to oral antibiotics once they improve clinically and blood parameters improve.[25] Adequate pain control is another important aspect in the management of osteomyelitis especially in the early stages.

Even with early diagnosis and proper treatment, orthopedic sequelae of neonatal osteomyelitis are common which include cartilaginous growth plate destruction with discrepant limb length, angular deformity, pathologic fractures, arthritis, femoral condyle erosion, and limb palsy.[10] These changes can progress so a delayed diagnosis or inadequate treatment increases the risk for sequelae. Thus, all neonates with osteomyelitis should have careful outpatient follow-up for early detection of long-term orthopedic sequelae.

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 Pediatric Journal

Case Report

Subaponeurotic fluid collection – An unusual cause of scalp swelling in infancy

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ABSTRACT

Subaponeurotic fluid collection (SFC) is a rare cause of scalp swelling in infants that is not well described in textbooks. It can be diagnosed clinically and managed conservatively. We report two infants, who had scalp swelling, with findings suggestive of SFC that resolved spontaneously. We have reviewed literature on the possible mechanisms of fluid collection. We wish to highlight the self-limiting nature of this condition so that unnecessary investigations, referrals, and interventions are avoided.

Keywords: Subaponeurotic fluid collection, Infant, Scalp swelling

INTRODUCTION

Scalp swellings are quite common in the newborn and the causes include cephalhematoma and caput succedaneum. Similar swellings beyond the newborn period cause anxiety among parents and treating pediatricians. Subaponeurotic fluid collection (SFC) as a cause of scalp swelling is not well described in textbooks.[1] It runs a benign course and resolves spontaneously. Awareness about this condition among pediatricians is essential, to avoid unnecessary investigations, referrals, and interventions. We report two infants, who presented scalp swelling, which was diagnosed clinically as SFC and managed conservatively with complete resolution of swelling.

CASE DESCRIPTION

Case 1 was a boy aged 11 weeks, born by normal vaginal delivery, and Case 2, a girl aged 9 weeks born by emergency LSCS – because of arrest of labor. Both presented with an ill-defined scalp swelling of 1-day duration [Figures 1 and 2]. There was no history of forceps or ventouse history of application before delivery or fetal scalp electrode placement. In both infants, there was no bruising, scalp swelling, or cephalhematoma in the immediate newborn period. On examination, both had soft, non-tender, fluctuant swellings not limited by suture lines in the parieto-occipital region. A fluid shift was noted on head movement. The hemoglobin level, platelet count, and clotting profile were normal.

In both, a clinical diagnosis of SFC was made. Ultrasound of the head confirmed the diagnosis [Figures 3 and 4]. The parents were reassured and in both, there was a spontaneous resolution of the swelling over the next 6–8 weeks.

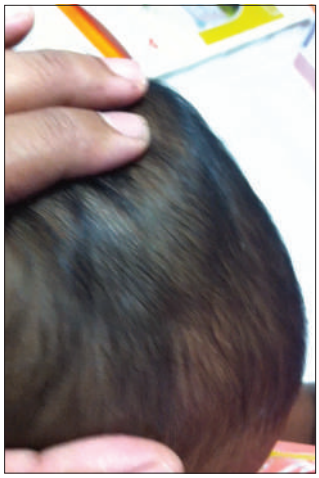

Figure 1: Scalp swelling in Case 1.

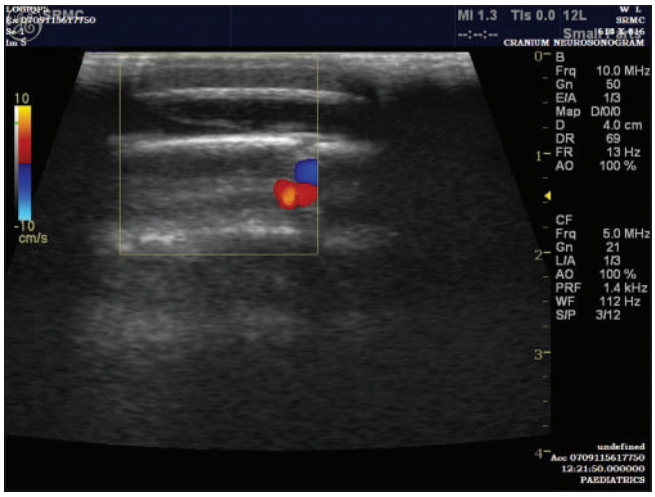

Figure 2: Ultrasound sonography showing subaponeurotic fluid collection in case 1.

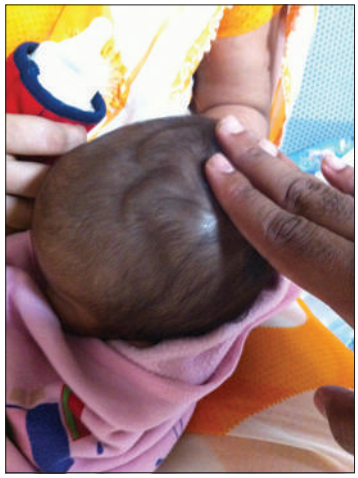

Figure 3: Scalp swelling in case 2.

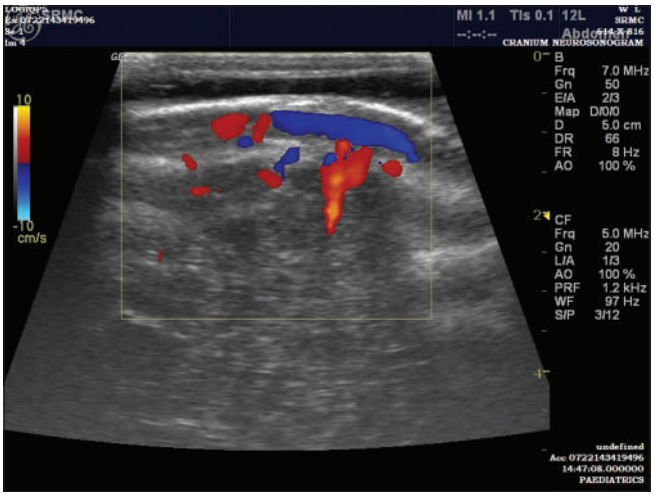

Figure 4: Ultrasound Sonography showing subaponeurotic fluid collection in case 2.

DISCUSSION

SFC is a rare clinical entity that presents in infancy, weeks after birth. They are soft, compressible, cystic swellings that usually cross the suture lines. Fluctuation and fluid thrill can be elicited. The cause of SFC has not been clearly defined. The fluid collection is cerebrospinal fluid (CSF) but the exact mechanism behind this leakage is not clear. Schoberer *et al*. reported a series of five cases of SFCs in which the fluid was aspirated in three and, in all three, the fluid reaccumulated. The fluid was serosanguinous. The β2-transferrin and β-trace proteins indicated the presence of CSF. They postulated that the CSF collection may be due to microfractures or disruption of emissary or diploic veins that connect intracranial venous sinuses with superficial veins of the scalp.[2] It has also been suggested that SFCs can occur because of birth trauma including vacuum delivery[3] and fetal scalp electrode placement[4] but SFCs without any risk factor have also been described.[3] In both the infants, we report here, there was no history of birth trauma or fetal scalp electrode monitoring.

Characteristic nature of the swelling aids in clinical diagnosis, without any radiological investigations.[5] The differential diagnosis includes non-accidental or accidental head injury and coagulation disorders, leading to subaponeurotic hemorrhage. In SFCs, infants appear well, whereas in subaponeurotic hemorrhage, they appear unwell.

The management of SFCs is conservative. Aspiration of the fluid is not helpful therapeutically, as the fluid reaccumulates after aspiration as reported in previous case series.[2] Most of the SFCs resolve spontaneously without any intervention, as in our study infants. However, if the swelling persists beyond

3 months without signs of resolution, MRI can be done to rule to CSF fistula.[6]

CONCLUSION

SFC is a rare cause of scalp swelling in infants and can occur without any risk factors. It can be diagnosed clinically. Management is watchful expectancy, without any intervention and parental counseling about the benign nature of the swelling. They resolve spontaneously in 6–8 weeks.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Source: Hauta-Alus HH, Holmlund-Suila EM, Kajantie E, Rosendahl J, Valkama SM, Enlund-Cerullo M, Andersson S, Mäkitie O. ***The Effects of Vitamin D Supplementation During Infancy on Growth During the First Two Years of Life.*** The Journal of Clinical Endocrinology & Metabolism. 2020 Dec 21., dgaa943, https://doi.org/10.1210/clinem/dgaa943

In this randomized, double-blinded intervention study, researchers sought to examine how maternal and child 25-hydroxyvitamin D (25(OH)D) and Vitamin D supplementation impact growth during the first 2 years of life. The authors discovered that toddlers born to mothers with pregnancy 25(OH)D >125 nmol/L were at 2 years lighter and thinner compared with the reference group with 25(OH)D 50–74.9 nmol/L. Toddlers in the highest quartile of 25(OH)D were shorter, lighter, and thinner compared with the lowest quartile. There may be an inverse U-shaped relationship with Vitamin D and early childhood growth.

Source: Yilmaz Bayer O, Turktas I, Ertoy Karagol HI, Soysal S, Yapar D**.** ***Neuropsychiatric adverse drug reactions induced by montelukast in children with asthma impair the quality of life***. Journal of Asthma**.** 2020 Dec 8:1-4. https://doi.org/10.1080/02770903.2020.1861626

In patients taking montelukast due to asthma, the researchers sought to detect the neuropsychiatric adverse drug reactions (ADRs) that occurred in real time and to test the impact of these ADRs on quality of life (QoL). Patients aged 3–18 years who first took montelukast and their parents were included. The neuropsychiatric complaint assessment questionnaire and the KINDL QoL scale were administered to patients and their parents at the beginning of the study and at the end of the 2nd week of treatment. Multivariable logistic regression tested the impact of ADRs on the decrease in QoL. In 78 (62.4%) of 125 patients who recovered when the drug was withdrawn, neuropsychiatric ADRs were reported. Compared with pre-treatment, temperamental behavior, nightmares, and sleep disorders occurred significantly more often in both groups. Significant decreases were found in both child and parent proxy-reported QoL total/sub-scores compared with pre-treatment in both groups, except in the child-reported family relationships subscale in the school-age group. Neuropsychiatric ADRs induced by montelukast are more common than recorded in the literature and negatively affect the QoL of children.

Source; Auger N, Soullane S, Luu TM, Lee GE, Wei SQ, Quach C. ***Association of Cesarean Delivery with Childhood Hospitalization for Infections before 13 Years of Age***. The Journal of Pediatrics.2020 Dec 21: ARTICLE IN PRESS. https://doi.org/10.1016/j.jpeds.2020.12.036

Researchers conducted a longitudinal cohort study of 731,803 children born between 2006 and 2016 at all hospitals in Quebec, Canada, with the aim to examine the correlation between cesarean delivery and childhood infection up to 13 years of age. Relative to non-operative vaginal delivery, cesarean delivery is correlated with 1.07 times the risk of otitis media, 1.15 times the risk of respiratory infection, and 1.13 times the risk of infectious enteritis at 3–4 years of age.

Observations revealed correlation of cesarean delivery with infection hospitalization before but not after 5 years of age. However, operative vaginal deliveries also exhibited the associations, which suggests that mechanisms other than exposure to maternal vaginal flora explain the relationship.

Source: O'Keeffe LM, Frysz M, Bell JA, Howe LD, Fraser A. ***Puberty timing and adiposity change across childhood and adolescence: disentangling cause and consequence***. Human Reproduction. 2020 Dec;35(12):2784-92. https://doi.org/10.1093/humrep/deaa213

Researchers examined if earlier puberty is more likely a result of adiposity gain in childhood than a cause of adiposity gain in adulthood through performing a prospective birth cohort study of 4176 individuals born in 1991/1992 with 18,232 repeated estimates of fat mass from age 9 to 18 years. Repeated measures of height from 5 to 20 years were employed to determine puberty timing (age at peak height velocity) and repeated measures of directly measured fat mass from age 9–18 years, from a contemporary UK birth cohort study, were used to model fat mass trajectories by chronological age and by time before and after puberty onset. Findings support correlation of prepubertal fat mass with earlier puberty timing but there appeared no correlation of puberty timing with post-pubertal fat mass change. Among females, earlier puberty timing is more frequently a result of adiposity gain in childhood than being a cause of adiposity gain in adulthood. In males, disparities in fat mass after puberty are driven partially by tracking of adiposity from early childhood as well as by higher gains in post-pubertal adiposity in males earlier to puberty. Overall findings support implementing interventions aimed at lowering levels of childhood adiposity as valuable to avert earlier puberty, adult adiposity, and their adverse health outcomes in both females and males.

Source: Chong PF, Kira R, Torisu H, Yasumoto S, Okumura A, Mori H, Tanaka-Taya K, Sato T, Kanazawa A, Suzuki K, Toyofuku E. ***Three-year longitudinal motor function and disability level of acute flaccid myelitis***. Pediatric Neurology. 2020 Dec 3. ARTICLE IN PRESS. https://doi.org/10.1016/j.pediatrneurol.2020.11.019

In a cluster of pediatric patients with acute flaccid myelitis (AFM) associated with the enterovirus D68 (EV-D68) outbreak in 2015, researchers sought to describe the long-term motor outcome and disability level. At the acute (nadir), recovery (6 months), and chronic (3 years) stages, clinical data, including the motor function (manual muscle strength test) and other neurological symptoms, were gathered for this nationwide follow-up questionnaire analysis study. Clinical data were available for 33 AFM patients (13 females, 20 males; median age = 4.1 years). Among patients with tetraplegia or triplegia, paraplegia, and monoplegia at the acute stage, 2/7, 4/13, and 2/13 showed complete recovery without paralysis, out of those 5/7, 8/13, and 2/13 who noted improvement with lesser limb involvement at the chronic stage, respectively. AFM has a high rate of persistent motor deficits of 1–2 limb paralysis. However, disability level of patients with AFM usually improved at 3 years.

Source: Lukomskyj, N, Shi, Y, Allman-Farinelli, M, Rangan, A. ***Associations between breakfast consumption from childhood to adulthood and cardiometabolic health***: A systematic review. *Nutrition & Dietetics*. 2020; 1–18. https://doi.org/10.1111/1747-0080.12647

This systematic review examined data from cohort studies on the relationships between childhood to adulthood breakfast consumption and cardiometabolic health. Seven databases have been searched; eligible records covered analyses assessing breakfast consumption in childhood and adulthood, and type 2 diabetes, cardiovascular disease, obesity, or related clinical risk factors. Six eligible articles, representing four cohort studies from two countries, have been reviewed. Most articles found important connections between breakfast consumption in childhood and adulthood and cardiometabolic benefits, but the quality of evidence was low. Childhood and adulthood breakfast intake were each correlated with cardiometabolic benefits, and breakfast consumption over both life stages was related to greater benefits. Increased breakfast intake from childhood to adulthood has also been associated with cardiometabolic benefits.

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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