B D R News

The official newsletter of the Birth Defect Registry of India,
(A unit of Fetal Care Research Foundation)

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Proceedings of the Birth Defects Registry meetings held on 23.08.2009 & 19.11.2009

The third & the final meeting of the current year were held on 2308.09 & 19.11.2009 respectively at MediScan systems premises, Chennai. The topic dealt in the third CME session was "Antenatal Diagnosis & Postnatal Management of Congenital Adrenal Hyperplasia" (CAH). Dr. Suresh at the outset welcomed the members who had gathered in appreciable number for the meeting. He acknowledged the efforts of BDRI for having analyzed over 5 lakh births during the past 8 years & repeatedly appealed to all members to motivate more hospitals to join the mission. FOGSI BDR members meticulously contributing data to the registry were appreciated. While discussing the importance of Newborn screening (NBS) as a mandatory protocol for the newborns, he said that early diagnosis facilitates better management & outcome. NBS is universally recognized and practiced in many parts of the globe. He appealed to members to be a part of the NIAAMS - National Initiative for Aneuploidy Anomaly & Metabolic Screening network to bring down the incidence of the preventable birth defects & also provide supportive care to those born with specific metabolic disorders. By joining the network, a member can get complete guidance for the implementation of NBS / Aneuploidy Screening program in maternity hospitals & interpretation of results obtained for appropriate action. This network on national basis will facilitate the creation of a single database for many congenital problems in the future. (More details in last page)

The final meeting of the BDRI for the year threw light on the recent advances in the management of Congenital problems of Ear, Nose & Throat. Dr. Suresh extended a warm welcome to the guest speaker Professor. Mohan Kameswaran, Founder, Director Madras ENT Research Foundation. He mentioned that antenatally the sonologist would look for the nasal bone & midline defects such as holoprosencephaly. Ears & throat are not routinely looked for anomalies though vocal cords can be seen by ultrasound. He lauded Dr. Mohan for his pioneering work on cochlear & many other innovative implants in Asia & facilitating hearing faculty for the affected.

Following are the excerpts of the presentations made at the CME session on CAH & the Management of Congenital ENT problems.

Antenatal diagnosis of Congenital Adrenal Hyperplasia (CAH)
(Dr. Pooja Vazirani, Fellow, Fetal medicine, MediScan)

Dr. Pooja commenced her talk saying that CAH is one of the fetal endocrine problems due to disorders of steroidogenesis. Congenital adrenal hyperplasia diagnosed in the fetus is an autosomal recessive disorder and the incidence is found to be 1/15000 births. It is caused by the deficiency of one of the five enzymes such as 1) 21 Hydroxylase 2) 11 Beta Hydroxylase 3) 3 Beta Hydroxy Dehydrogenase 4) 17 alpha Hydroxylase & 5) P450scc. Of the 5 enzyme deficiencies, more than 90% is caused by 21 Hydroxylase deficiency. While CAH due to 11 Beta Hydroxylase is not common, CAH due to 3 Beta hydroxy dehydroxygenase is very rare. In steroid synthesis, genes such as CYP21A & B are needed for the production of 21 Hydroxylase. These are located within the HLA DR complex on the short arm of chromosome.Genetic mutation in CYP21 A & B results in decreased synthesis of Cortisol & Aldosterone, peaking the levels of Androstenedione & Testosterone causing virilisation of the female genitalia.

The **phenotypic presentation** may be **classic** or **non classic**. The classic type in females presents as enlarged clitoris with fused labia, anteriorly placed vaginal orifice which is identified at birth due to virilisation. Male babies with CAH of salt losing type presents with vomiting, dehydration, poor feeding, hyponatremia & hyperkalemia in the newborn period. In such situations CAH may be detected within 4 - 7 days. In non classic type, the affected remain asymptomatic till their adolescence. Females present with increased growth rate, abnormal menses, acne & hirsuitism. Males have tall stature & are diagnosed much later may be at the time of their marriage. CAH may also be grouped in to 3 types in relation to the enzyme activity - 1) Salt losing type presents when there is total loss of enzyme 2) Simple virilisation when the enzyme activity is 1 - 2% of the normal range & 3) Non classic when 20-60% of enzyme activity is present in phenotypes.

The common **diagnostic tool** used in the 70s & 80s for prenatal diagnosis was the estimation of 17 OHP levels in amniotic fluid. In late1980s CVS revealed the sex & ambiguity by DNA linkage analysis & now direct DNA analysis for CYP 21 gene mutation in the fetal cells / tissues is the order of the day.

Prenatal Diagnosis of CAH is possible depending on the scenarios as explained: CAH as with any autosomal recessive condition has a 25% recurrence risk in every pregnancy.
1) When proband (index case) is present, prenatal diagnosis of CAH is easy & quicker when compared to a situation where the proband is absent or does not exist. Molecular confirmation by establishing the CYP21 mutation in the child & the parents's carrier status is determined prior to prenatal diagnosis. The family is also extensively counseled by the Geneticist regarding the recurrence risk in subsequent pregnancies. Since the mutation of the fetus can be identified through prenatal procedures, the option of continuing / discontinuing the pregnancy is left to the choice of the parents.

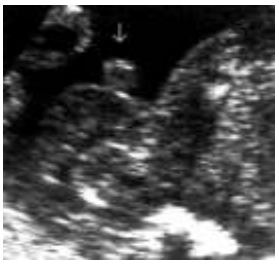
If they want to continue pregnancy despite the fetus being affected, the need for starting the mother on dexamethasone therapy by 6-8 weeks of pregnancy is emphasized. This can only prevent virilisation of the clitoris in the female child & will not cure the disease. Chorionic villi sampling (CVS) between 11-13 weeks of pregnancy or amniocentesis between 16-20 weeks of pregnancy is done for prenatal diagnosis. KT / FISH / 17OHP level estimation & mutation analysis can be done in the prenatal samples.

2) When proband is not present & parental carrier status could not be ascertained due to cost factor, it is wise to start the mother with a history of previous CAH child on Dexamethasone therapy (20mcg/kg/day). Dexamethasone started beyond 8 weeks will not have any effect on virilisation of genitalia. Karyotyping & 17OHP level estimation in amniotic fluid are done by 16-20 weeks of pregnancy. However postnatal investigations are required to confirm or rule out the problem in the child. With the advent of recent advancement such as amplification of free fetal DNA in maternal plasma uses sex determining region Y (SRY) gene as a marker for the fetal Y chromosome. This can be done if the facility is available as early as 6 weeks of gestation. It is a non invasive test to identify the sex of the fetus and is helpful in deciding the dexamethasone therapy.

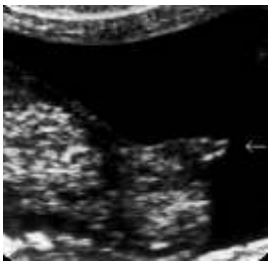
3) If the mother is a known case of CAH (simple virilising type) and the partner is normal, 50% of her offspring will be carriers for the mutation. If the partner is a carrier, there is 50% recurrence risk for the offspring to inherit the problem. However, mother's 17 OHP should be maintained at optimal levels during pregnancy by treating her for hyperandrogenemia. This would prevent virilisation even if the fetus is found to be a female & unaffected by prenatal diagnosis, of the genitalia in the fetus. Presence of male genitalia either does not rule out CAH in the fetus. Only postnatal work up can provide a definitive answer. The role of NBS can not be exaggerated in such situations.

4) Antenatal ultrasound diagnosis of ambiguous genitalia in the fetus without any previous history warrants further diagnostic investigations - Karyotyping of the fetus, 17OHP level, NBS & further molecular confirmation are needed for effective management after birth.

Cases were well illustrated to explain the advantages of identifying the DNA in the proband & the carrier status of the parents for prenatal diagnosis. In situations where mutation is not known, identification of genitalia is important in target scan. Ultrasound imaging of the external genitalia is tricky. It is differentiated only after 12 weeks. During the embryo stage, the genital tubercle formed gets differentiated into clitoris in females & phallus in males. Some studies say that position of phallus in males is at 45-90 degrees & the clitoris is at 180 degrees. This provides clues for ambiguity of genitalia between 11-14 weeks scan.



Phallus 45 – 95 degree

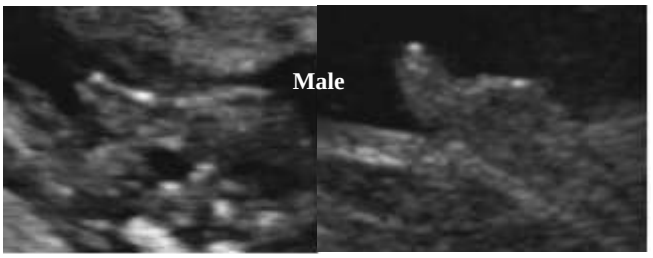


Clitoris – 180 degree

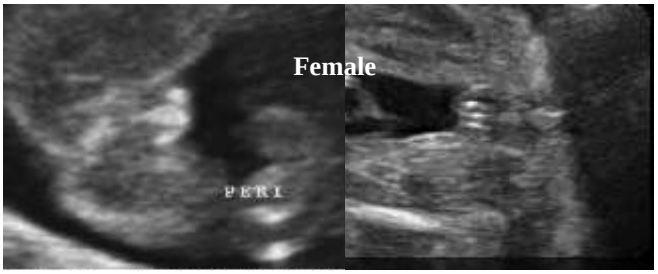
Testis descends after 26 weeks & in 20-30% of cases, it happens only after 26 weeks. When there is micropenis with undescended testes it appears similar to clitoromegaly. It is hard to define accurately the findings such as micropenis with cryptorchidism & clitoromegaly with normal labia. It is wise to be cautious in wording the diagnosis. It may be reported as ambiguous genitalia & investigated further to arrive at a conclusion.

Karyotyping is essential. If the sex is male, consider the other possibilities of hypospadias and bifid scrotum. If the fetus is a female & the USG suggests - (fused labioscrotal folds, clitoromegaly) male genitalia, CAH should be suspected & investigated further.

Imaging normal genitalia

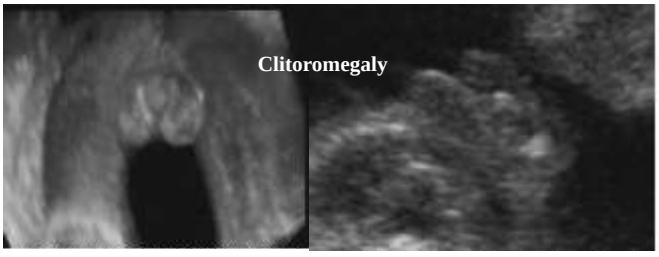


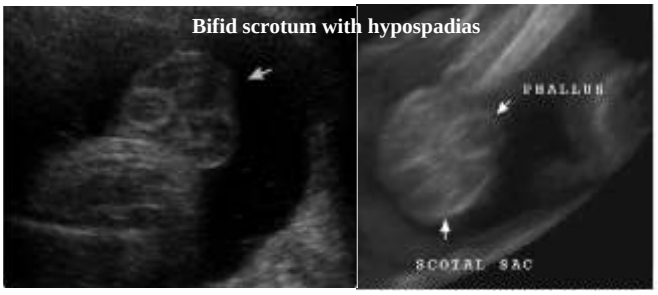
17 weeks **22 - 23 weeks**



18 - 19 weeks **22 - 23 weeks**

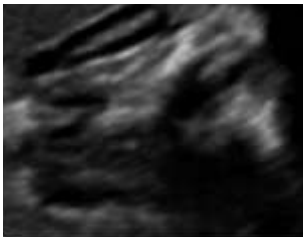
Imaging CAH





Genetic counseling plays a crucial role in convincing the family concerned about the need for investigations, costs involved, and limitations of USG & the possibility of a diagnosis at later gestation.

While quoting journal references about the recent advancements in imaging the adrenals by ultrasound as an advanced technique to diagnose CAH, the speaker mentioned that more studies need to be done to use this as a diagnostic tool for CAH.



Normally adrenals are seen in II trimester, capping the upper pole of kidneys with large hypoechoic cortex & thin echogenic medulla. Adrenals were said to appear as cerebrum shaped with sulci & gyri (hyperechoic) & enlarged even in the absence of ambiguous genitalia in male babies with salt losing type of CAH.

Differential diagnosis of ambiguous genitalia in a male fetus may be :

1. 5 alpha reductase deficiency, 2.Smith lemli Opitz (SLO) disorder
3. Drash syndrome, 4.Camptomelic dysplasia ,
5.Androgen nsensitivity syndrome, 6. Frasier syndrome

Other types of CAH are less common. Most of them will have ambiguous genitalia & salt wasting may or may not be present. In the absence of CYP21 mutation and ambiguous genitalia other enzymes are to be tested before venturing in to differential diagnosis.

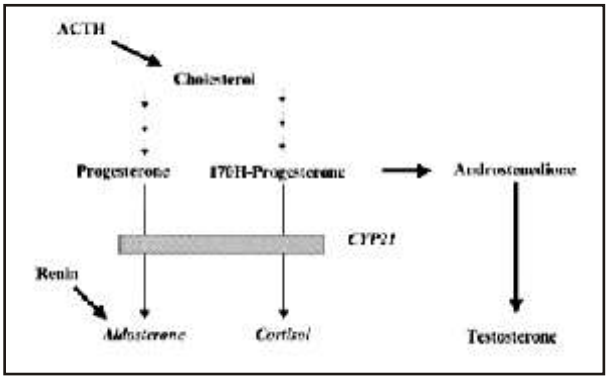
The talk concluded with the following **take home messages:**

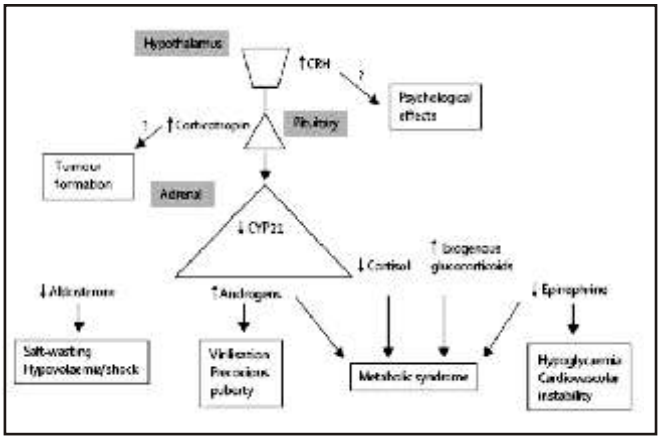
- CAH is the most common cause of ambiguous genitalia
- Carrier status of the parents/ Index case work up are important
- Prenatal diagnosis is available if diagnosed
- Report as ambiguous genitalia if not sure
- Cases of ambiguous genitalia with no prior history require genetic counseling and work up

Medical Management of Congenital Adrenal Hyperplasia

(Dr. Shriraam mahadevan, Consultant Endocrinologist, Associate in Clinical Endocrinology, Education and Research (ACEER), Chennai

Dr. Shriraam Mahadevan talked about the clinical presentation & the medical management of CAH in children & adolescents in general. As CAH due to 21 Hydroxylase enzyme deficiency forms > 90% of cases, he focused on this subject alone. Briefly going through the pathophysiology, he said that the so called bad cholesterol - LDL is necessary for the production of life saving cortisol & sex hormones in the body.





The adrenal cortex absorbs the dietary cholesterol and converts it into 3 types of steroids namely, minerelorticoid-aldosterone, glucocorticoids - cortisol & testosterone-male hormone. Incidentally females also produce Testosterone from the adrenals & ovaries to some extent. The DHEA-adrenal specific androgen is produced in large amounts in CAH due to the block in the production pathway of aldosterone & cortisol.

Excessive production or diversion of precursors increases the target hormone ACTH depicting the classic endocrine feedback mechanism. Cortisol maintains the hormonal feedback mechanism by suppressing the pituitary gland & ACTH production. When the target hormone- cortisol level decreases due to enzyme deficiency, the trophic hormone ACTH level increases.

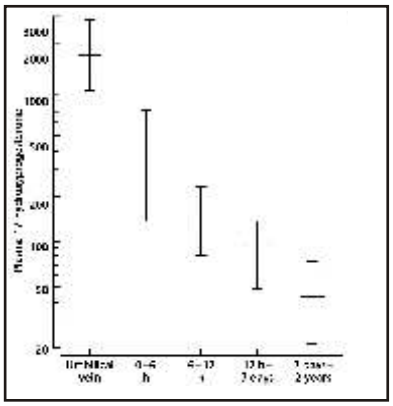
The excess of ACTH causes the dark pigmentation in CAH & increased androgen production leading to androgenic effect-virilisation in female fetuses. Hence the management of CAH lies in bringing about a balance of the 2 deficient hormones & 1 excess hormone which is surely a tricky solution.

CAH as discussed can be classified as classic & non classic depending on the spectrum of symptoms presenting with the condition. Total loss of 17 OHP presents with classic variety & partial loss leads to non classic symptoms .Individuals with non classic variety are heterozygote carriers who are generally missed. Simple virilising type of CAH would present clinically as below during various phases of life.

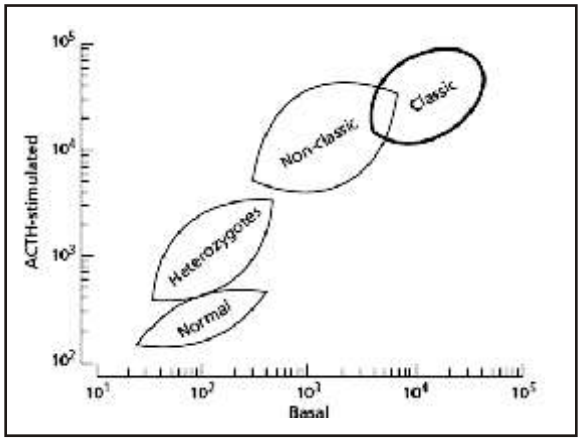
Growth Phases	Genetic Females	Genetic Males
Newborn Period	Ambiguity Salt Crisis	Salt Crisis Simple virilizer (asymptomatic)
Early Childhood	Precocity(heterosexual) Accelerated Growth Premature Pubarche	Premature Pubarche /enlarging genitals Accelerated growth Precocity(iso sexual)
Adults	Delayed puberty PCOS like presentation Sub fertility Adrenal masses	Short stature Adrenal rests in testis-sub fertility Adrenal masses

One simple dictum in diagnosis of CAH is, there can not be an enzymatic defect presenting with another genetic / chromosomal abnormality. It is relatively easier to pick up the classic CAH cases clinically presenting with ambiguous genitalia and / or salt wasting condition in the newborn period. Males may remain unsymptomatic but for the salt crisis & hence this justifies the importance of Newborn Screening. NBS may provide false positive values in situations like preterm birth, sampling before 72 hours of birth &sepsis / severe sickness.

As for non classic cases, an asymptomatic CAH carrier can give birth to a classic CAH baby. Males are tall as children due to androgenic influence but mostly remain as stunted adults as their bones fuse earlier than others. As with TSH, 17 OHP level stabilizes after 12 hours to 7 days after birth.



The normograms are based on ACTH stimulated 17 OHP levels. If this estimation is unavailable, basal values of 17 OHP is estimated. ACTH stimulation with 250mcg is required occasionally in non classic patients. There may be an overlapping of values as shown.



At present due to heavy cost involved, only basal 17OHP is estimated for diagnostic confirmation. In classic cases it would be >100ng/ml. Unstimulated 17OHP > 20-50ng/ml in adults, with low cortisol is diagnostic of CAH. Other corroborative evidences may include increased levels of Testosterone, DHEAS, Rennin & low Aldosterone. Ultrasound presentation (Mullerian structures / other anomalies), Karyotype, Mutation analysis & rarely CT/MRI also help in confirming the diagnosis. In males whose genitals are normal, other conditions such as Pyloric stenosis, Gastroenteritis(common), sepsis, pseudoaldosteronism, Congenital adrenal hypoplasia & isolated mineralocorticoid synthesis defects mimick CAH. In these conditions androgen excess will not be seen but the other two hormones will be elevated.

Management of CAH calls for early & accurate diagnosis at birth. Thereafter the child should be put on appropriate glucocorticoid & meneralocorticoid replacement. Sex assignment & plans for surgery should also be done in cases warranted. CAH females should be reared as females' only as normal puberty & fertility is assured in them. Long term monitoring for satisfactory growth parameters is also required here. There are parents wanting to grow females as males may be due to social factors but it is not desirable to do so.

Treatment of CAH is life saving initially & it is life long to normalize the electrolytes & hormones. Glucocorticoids is given to suppress the increase in ACTH & keep it in normal levels. Mineralocortocoid replacement may be necessary to sustain normal electrolyte homeostasis. Treatment should help maintain growth velocity & skeletal maturation.

Glucocorticoid Replacement

For children cortisol-Hydrocortisone 10-20mg/m2/day in 3 divided doses is preferred keeping in mind the physiological secretion of 6-7mg/m2/day. Cortisol is required for the functioning of adrenal medulla that secretes epinephrine & nor epinephrine in response to stress which will be absent in CAH. Under dosing may lead to crisis & hence slight over dosing is done to be on the safer side despite the side effects. Cortisone should not be used which has only 80% bioavailability & 66% potency. Also Dexamethasone, Prednisone should be avoided. Older adolescents & adults may use them. Men with adrenal rest require higher doses of Dexametahsone.

While monitoring CAH patients on Glucocorticoid therapy, one should look for symptomatic improvement, maintenance of normal levels of 17 OHP & Testosterone,electrolytes, annual bone age & careful monitoring of linear growth. Renin & Aldosterone maintenance are not considered as per the Western standards due to test availability & cost. Samples for hormones estimation should be collected at 8am. The target 17OHP should be checked at least 2-3 times a year & maintained between 4-10ng/ml. Level >10ng/ml of the hormone indicates androgen excess & it warrants dosage correction. .

Stress dosing needs a special mention in the management of CAH. Parents & Caretakers should understand the need for additional glucocorticoids during illness & stress conditions in order to avoid an adrenal crisis which may be life threatening. It is wiser to educate them to administer higher doses or IM Hydrocortisone to patients in stress conditions before Hospitalization. IV Hydrocortisone 100mg/m2/day in divided doses are given during such situations. Usually doubling or tripling of the daily dosage would be sufficient.

Mineralocorticoid Replacement

Infants with salt wasting usually need 0.1-0.2 mg of Fludrocortisone which is now available locally at a reasonable cost. This supplementation may decrease after early infancy. It is also given to simple virilisers for Glucocorticoid sparing effect.

Long term follow up involves monitoring patients for adequacy of dosing of both gluco & mineralo corticoids. Careful titration is essential as both excess & inadequacy can

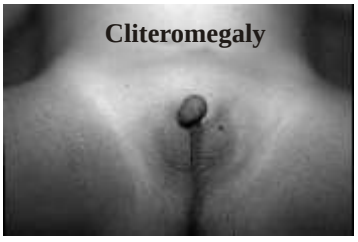
Trigger many problems. CAH girls who are non complaint to treatment may attain premature pubarche due to fluctuations in steroid dosage. The management in such cases becomes more complex. Inadequate Glucocrticoid results in symptoms of adrenal insufficiency (eg anorexia, nausea, vomiting, abdominal pain, asthenia) and will result in progressive virilisation & advancement of skeletal maturation in virilising forms of CAH. Excess dosage will lead to weight gain, cushingoid features, hypertension, hyperglycemia,cataracts & growth failure. On the whole a team comprising of Endocrinologist, Surgeon, Geneticist, Obstetrician and Gynecologist & Psychologist is needed to provide quality life to CAH patients.

If monitored well, individuals go through normal puberty. The speaker provided clues to Gynaecologists for diagnosing the Non Classic CAH (NCCAH) females with the following clinical scenario. When a lean, short female born to consanguineous parents, presents with PCOS picture-hirsuitism, acne, oiligo / amenorrhoea or premature pubarche, CAH may be thought of & it warrants 17 OHP estimation. If it is > 2ng/ml, stimulated ACTH level > 10ng/ml confirms NCCAH in the patient. Although mutation testing is available, it is less expensive to confirm the diagnosis by these estimations. Treating them with a mild steroid would be greatly beneficial for suppressing ACTH, normalizing the menstrual cycles & hirsuitism he added. Dr. Shriraam concluded saying that balancing Hyperandrogenism & Hypercortisolism is the job of treating endocrine physician in CAH. Since CAH due to 21 Hydroxylase deficiency has a clinical spectrum with variable presentations, long term monitoring of children especially during growing years by appropriate steroid replacement, optimization of growth, follow up during adolescence to watch for hyperandrogenemia and its consequences (PCOS & subfertility) & long term follow up for adrenal rests or other tumors comprise of the overall management principles of the condition.

Redefining the role of surgery in CAH

Dr. V.Sripathi, Consultant Paediatric Urologist, Chennai

Dr. V. Sripathy while speaking on the topic mentioned that though diagnosis & treatment of CAH are difficult issues more complex is the surgical correction & its long term implications. Surgical problems in CAH are due to 1) large clitoris resembling a penis 2) Urogenital sinus (variable length of union of vagina & urethra) and 3) fused labioscrotal folds (of variable length).While explaining the need for surgical correction, he said that the parents are concerned as there is a gender confusion in their offspring, fear of social acceptance & embarrassment to even changing nappy in public . Surgery also helps to avoid pooling of urine in vagina causing frequent urinary infections. Clinically cliteromegaly is thought to be inappropriate when the prepubertal glans clitoris is 3mm in width, or >10mm in width in the adolescence. Rule of thumb is when the thighs are kept together & if the glans is visible it denotes abnormality. Clinical diagnosis is made at the sight of ambiguous genitalia.

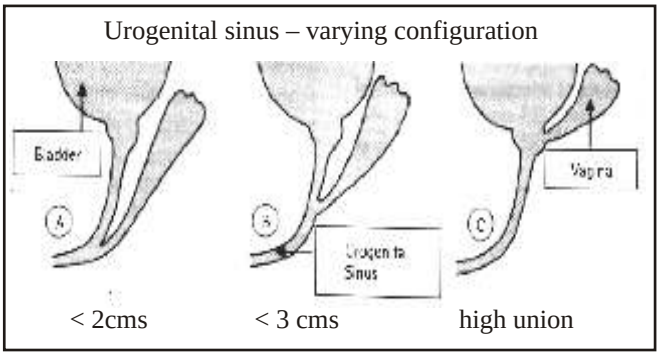


Cliteromegaly

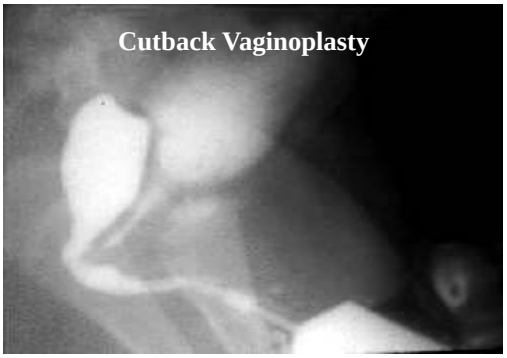
When gonads are not palpable in the labioscrotal folds, rectal examination with the little finger to feel the uterus in midline provides a clue to diagnosis of CAH in the baby. This is helpful in the absence of salt wasting symptom. Labioscrotal fusion is diagnosed by measuring the ano- genital distance and if the distance from anus to fourchette divided by the distance from anus to base of clitoris ratio is > 0.5 labioscrotal fusion is evident.

Labioscrotal fusion

Timing of surgery is usually 2-3 months after birth or at 1-2 years of age. Presently there is a conflict to operate when the child is old enough to give consent. Separation of vagina & urethra depends on the level of confluence as shown



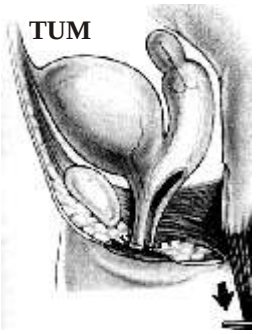
When it is low in confluence it is done within a few months, if high it may be separated at puberty when the vagina is thicker & easy to handle. Vaginal substitution with bowel segments is done only at puberty. This also facilitates self dilatation as the individual can be taught to do so at this stage rather than in early childhood when it causes a lot of pain & uneasiness.The level of urogenital confluence is measured using the genitogram. If the common channel is < 2cm, cut back vaginoplasty is done.



Cutback Vaginoplasty

Flap vaginoplasty is completed

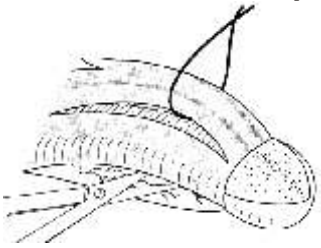
This can be performed in infancy & this does not require dilatation later. If the common channel is > 3cm, Total Urogenital Mobilisation (TUM) is done by pulling down the vaginal & urethral structures & separating the orifices in the perineum taking care to minimize the neurogenic damage. (See fig below)



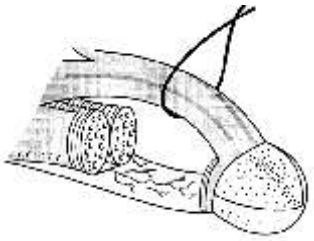
Though this can be done in infancy, it is better to be done at puberty when the tissues are stronger despite more loss of blood. If the common channel is longer than 3 cm, vaginal substitution is done using either the sigmoid colon or the ileum to bridge the gap before puberty.

There are controversial issues regarding vaginal surgeries mentioned. Recent evidence has shown that cliterodectomy done in the 60s has resulted in poor sexual arousal and loss of libido in adulthood. The surgeon emphasized the need to counsel at length the family before operating on the patient Surgical techniques have therefore been modified but controversies still persist which are fuelled by self help groups.The surgery of clitoral resection involves degloving of the clitoris, isolation of the neuro vascular bundle on to the dorsum, & separating it by dissecting up to the glans. The ventral mucosal strip is isolated, leaving the two corpora & the clitoris is recessed back onto the stump of the corpora at its normal location. Remaining skin is used to refashion the labial folds to give it a better appearance.

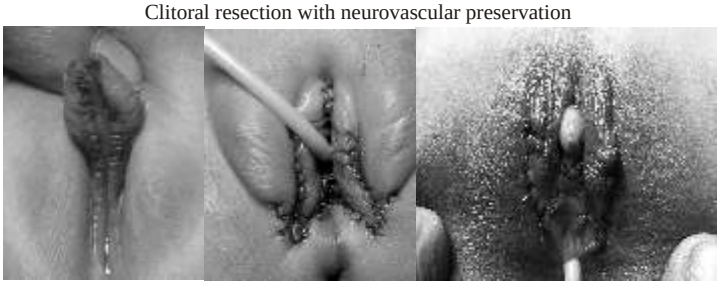
Isolation of neurovascular bundle and ventral mucosal strip



Division of corporal bodies

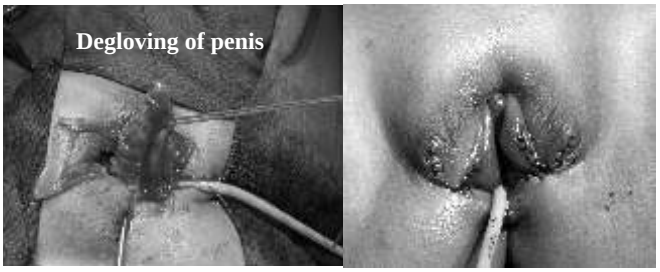


Clitoral resection with neurovascular preservation



The glans even if looks a little big, would get better during growth & with its rich nerve supply preserved. The complications of this surgery are sloughing or atrophy of glans due to traction of the nerves in spite of maximal efforts to preserve the nerve & blood supply. Even if the glans is preserved there may be loss of sensation. These issues may give rise to litigations in future. Dr. Sripathy cited the outcome of Cliteroplasty by quoting a study on 6 patients.2 had no clitoral tissue despite reduction,5 had problems during intercourse & all had abnormal responses to thermal and vibratory stimuli. (Genital sensation after feminising genitoplasty: A pilot study - Crouch NS, Minto CLBJUI 2004) Due to limitations of the 2 types of clitoral reduction mentioned, another technique came into vogue-Clitoral Recession by Plication. This involves degloving of the clitoris, maintaining the ventral mucosal strip & putting a series of plicating sutures with the corporal tissues remaining intact.

Clitoral Recession by Plication.



The problems that aroused due to clitoral recession were painful erections & snapping of plications in adulthood. Hence much better surgical techniques have been devised.

Corporal filleting technique is one such procedure where the erectile tissue is removed from within the corporal bodies after minimal dissection of nerves & blood vessels. An interesting video demonstration of the surgery using this technique was well illustrated. Other techniques used such as Banana Split, Subtunical Recession & their limitations were explained.

The following are the methods of assessing the clitoral sensation after the surgery:

1.Capillary Perfusion Test
2.Touch using cotton tip applicator
3.Thermal sensation using warm water
4.Vibratory sense using biothesiometer

The lecture ended with the “consensus statement on management of intersex disorders” that has been arrived at. (Journal od Paediatric Urology: 2006:2,148-162)

Conclusions

- In future the 'sexual awareness revolution' will determine the nature and timing of surgeries of this nature
- What has not been discussed is, if we wait for the child to make a decision what about ridicule from peers in School ? Will this not cause psychological trauma ?
- Surgery on clitoris only in Prader 3,4,5
- Surgery only by surgeons extremely familiar with technique of nerve and vessel preservation
- Separation of low confluence of vagina and urethra in infancy to avoid vaginal pooling of urine and peritonitis
- No vaginal dilatations during infancy and childhood Vaginal reassessment at puberty in low confluence cases
- Vaginal 'pull through' or “substitution' only at puberty

Finally as always emphasized, a 'Team approach' is needed in the treatment & management of CAH in the long run to provide quality life to the affected

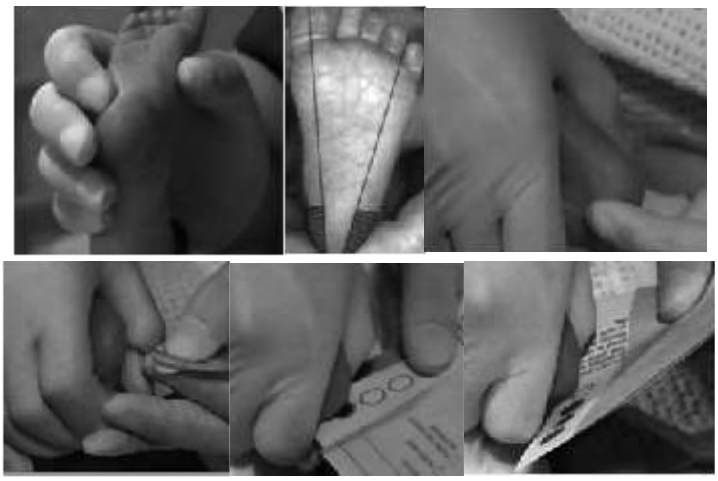
New born screening

Dr. Sujatha jagadeesh, Clinical geneticist, Mediscan

Dr. Sujatha Jagadeesh started by justifying the role of NBS in picking up the non classical CAH cases who are asymptomatic. Prevention & Prenatal diagnosis come later. Quoting the incidence of CAH to be quite high in our scenario, she said that it is a cost effective & reliable method of diagnosing the affected as early in the newborn period. If they are left undiagnosed & untreated, it leads to high morbidity & mortality later. If diagnosed, effective treatment can be offered. It also facilitates proper sex assignment, prevention of adrenal crisis & mortality. NBS worldwide reveals an incidence of 1/14000-1/18000 births approximately. Out of this, 66% have classical CAH &32% have simple virilising type of CAH. In some countries, the classical salt losers are detected in the first screening done at 72 hours after birth & the simple virilisers are detected in the second screening done in the second week after birth.

Sampling Methodology in NBS

Blood samples are to be collected from the neonate by trained technicians on FDA approved filter paper 72 hours after delivery. Special lancet is used to prick the lateral portion of the heal without squeezing, taking care to accurately drop the free flowing blood on to the circles in the filter paper wetting both sides. Over dropping is not allowed.



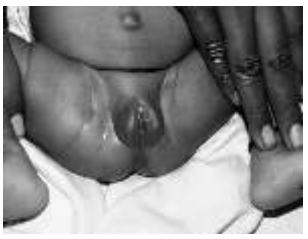
Dr. Sujatha mentioned that Fetal Care Research Foundation in collaboration with ICMR (Indian Council of Medical Research) has screened around 9000 babies born in the Government Hospital, Egmore, chennai during August 2008 till August 2009 for CAH & CH. Mediscan has also screened > 1500 newborns born in the private sector. The incidence was found to be 1/900 among those screened. This is quite high compared to the Western statistics available.

The protocol to be followed for the screen positives are 1) Repeat confirmation test 2) If found positive clinically examine the baby & get the other investigations (Karyotype, Pelvic Scan & other hormone levels) done. If the results are abnormal, treatment should be started & molecular confirmation has to be planned later. There lies still many dilemmas regarding the 1) Laboratory Cut Off values of 17OHP levels for confirmation. This could be standardized only when larger numbers are screened.

At present the values suggested are as follow: Negative<30nmol/L,Equivocal-30-90nmol/L,Positive->90nmol/L. 2) Confirmatory diagnosis by molecular assay considering the availability & cost 3)Whether to start cases of simple virilising on treatment 5) correct gestational weeks to assign preterm status as the NBS kit differs(27-34 weeks) from the ICMR definition of <34 weeks and whether 34-36 to be designated as full term?

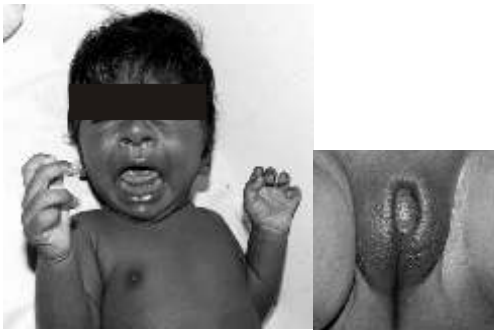
Three cases with both positive & negative results on NBS were discussed insisting the need for postnatal examination of the newborns who were screened.

Case 1:A full term (39 weeks) 2.2 kg female baby normally delivered by a mother who had uneventful antenatal period & did not take steroids. There was no consanguinity. This baby on screening had equivocal value for 17 OHP=47.1nmol/L. Repeat confirmatory testing turned positive with 115ng/ml (0.1-9.4). Her clinical examination one month after birth revealed absence of CAH symptoms (ambiguity, hyper pigmentation), with normal genitalia & no sign of virilisation.



This case turned out to be false positive but she requires continuous follow up for simple virilising type of CAH.

Case 2: A full term (39 weeks) female baby normally delivered was screen negative on NBS. There were no h/o maternal steroids. On clinical examination, she had clitoral hypertrophy & hyper pigmentation with no symptoms of salt wasting.



Repeat test for the serum enzyme showed 120ng/ml which was positive. She has been started on Hydrocortisones & Aldosterones and molecular testing has been planned to know the mutation. This was a false negative case.

Case 3: A 35 week old male baby with birth weight 1.84kg was screen positive with 17 OHP = 67.5nmol/L. Repeat confirmation showed 21.7ng/ml in serum. The child looking clinically normal has male genitalia & no salt losing signs. He has to be followed up for late onset symptoms & molecular testing is planned.

Dr. Sujatha appealed to all medical professionals who refer cases for NBS to Mediscan for follow up of their screen positive cases to evolve a common protocol for treatment & management as this is still in its nascent stage.

Discussion

1) Will there be under virilisation in males with CAH?
CAH males due to deficiencies of Desmolase & 17 alpha Hydroxylase will present with undervirilised genitalia. These babies will have salt wasting but their 17OHP will be in normal range giving a clue to look for other enzyme deficiencies in CAH.

2) CAH mutation if known has any bearing on Dexamethasone therapy in pregnancy?
There are many categories of mutations known in CAH. If the mutation accounts for late onset type of CAH, dexamethasone need not be administered as this will avoid subjecting the mother to side effects of such therapy.

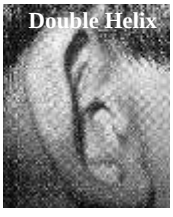
3) In general practice Beta methasone is given to mothers in Preterm labour. Will this affect the 17 OHP level in NBS?
Even a small dose of dexamethasone will have suppressing effect on cortisol for 48 hours. Hence if it is given for antenatal mother 48 hours before delivery, it will affect the level of 17 OHP in the neonate after delivery. Dexamethasone therapy is based on its effect across the placenta & suppress the ACTH to prevent virilisation. However NBS sample is taken only 72 hours after delivery. The ICMR study on NBS for CAH, also considers only full term babies born > 34 weeks for screening.

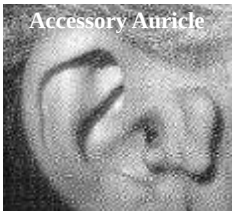
4) Do empirical steroids given for unexplained pregnancy loss / infertility before & during pregnancy (first 4 months) have any effect on the 17 OHP level?
Empirical steroids are not indicated for infertility anymore. Dexamethasone if started late-beyond 6 weeks will not have any effect as already mentioned. It may have side effects like weight gain, hyperglycemia in the mother. Some studies say that it may have some adverse effects on the fetus like low IQ/Cleftlip/Cleft Palate, but more studies are needed to confirm these reports.

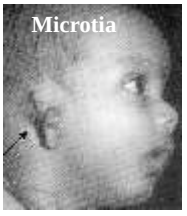
Congenital anomalies of Ear, Nose & Throat
(Professor Dr. Mohan Kameswaran, Madras ENT Research Foundation(MERF), Chennai)

Professor Dr. Mohan Kameswaran began his talk saying that although congenital speech & hearing problems are the commonest anomaly seen when compared to other birth defects, it has not been realized so as they are silent & not visible. When we see a blind or physically challenged person all our sympathies go to them naturally but it is not so with people who are born deaf-mute. But in today's world our life relies on the power of communication & hence it is important to rehabilitate the affected by detecting the problem early, correct & help them lead a life at par with the others.Hearing impairment is caused by abnormalities in external ear, middle ear or in the structure & functioning of the inner ear &/or the auditory pathways.

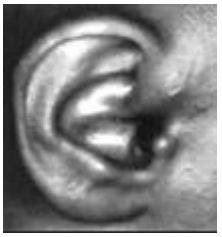
Diseases of the External Ear (Conductive Hearing Loss)
Common congenital exrenal ear malformations include the following Bat ear(Lop ear), Anotia, Microtia, Macrotia, Accessory Auricle & Pre Auricular Sinus or Fistula. **Bat or Prominent** ear does not cause any functional impairment & it is considered to bring in good luck rather! Prominent personalities like Mahatma had this feature. Correction if needed is done only for cosmetic reasons if the individual desires. For problems like **Anotia / Microtia**


Double Helix


Accessory Auricle


Microtia

(absence / small ears respectively) ear lobule is reconstructed using the costal cartilage by the age of 5 years. The ears get relocated when the skull grows and hence it is done around this period. When a child has bilateral anotia, it is warranted to test for normalcy of the cochlear function as both the inner & outer ear have different embryological sources. Both need not be impaired in the child & if the cochlea is intact, surgery & fixing of bone conduction hearing aids may be planned.



Pre auricular sinus are fistula is a blind track lined by squamous epithelium and opens in the ascending crus of helix and is formed due to improper fusion of the auricular tubercles. Sebacious material can get collected in the skin pit, get infected & cause painful swellings. This can be successfully treated by microscopic surgery.

Maetal Atresia is a birth defect characterized by hypoplasia of the external auditory canal often in association with dysmorphic features of the auricle, middle ear & occasionally the inner ear. The incidence is said to be 1/10000-20000 live births.

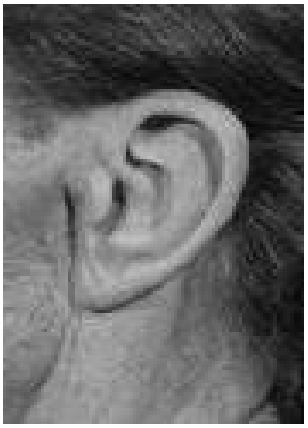
It is essential to first diagnose whether it is unilateral or bilateral & do the correction immediately. If delayed this can lead to speech impairment & poor IQ for hearing is an important aid to learning & acquiring knowledge. It is enough that one ear is repaired first if it is bilateral & then go in for permanent correction of both the ears. If it is unilateral, normal hearing in the other ear is ensured by testing & the correction is performed at the age of 5 by counseling the parents.The speaker cited the example of Alexander the great with unilateral hearing yet he was able to conquer the world.

Newborn Screening for Hearing is a common procedure in many countries across the Globe. Today it is possible to accurately assess hearing in newborn babies who are just one hour old! Sometimes meconium can occlude the ear canal & cause temporary hearing loss & in such babies follow up screening after a month would rule out the problem. Management of meatal atresia includes a bone conduction hearing aid, atresiaplasty & ossiculoplasty, Bone Anchored Hearing Aids (BAHA) or osseointegrated implants.

Bone Anchored Hearing Aids BAHA)

These work through direct bone conduction. Sound is conducted through the skull bone bypassing the outer & middle ear and stimulates the cochlea. New innovative osseo- integrated implants are the excellent prostheses used now. They are available in all shades of the skin to match the individuals & look real.

Osseointegrated Implant



Bone conduction hearing aid

It is fixed by a Titanium screw with the skull bone which facilitates easy removal & cleaning if needed. It alleviates the pain & inconvenience caused on the mastoids by hearing aids in the past. Many syndromes such as Down Syndrome, Treacher Collins syndrome are associated with problems of conductive hearing loss. Majority of Down children have hearing problems due to collection of fluid in the middle ear or collection of wax & rarely due to absent auditory meatus. Regular Screening procedures for hearing would help pick up & manage these problems in them. They look otherwise deceptive for hearing loss.

Diseases of the Internal Ear - (Sensory Neural Hearing Loss)

Congenital hearing loss in children may also be caused by defects in the sensory neural pathways of the ear. Of all types of sensory deprivation in the humans, hearing loss is the most amenable to correction. 99% of Sensory Neural Hearing Loss (SNHL) is caused due to cochlear pathology. The incidence is said to be 1/500-1/2000 as per the National statistics. According to a study conducted by MERF on > 600000 children below 12 years of age predominantly from rural areas of Tamilnadu., it was found to be 3.5/1000.

These figures are quite high when compared to other countries. The reasons may include high prevalence of consanguineous Marriages & other acquired reasons like Intrauterine infections (Rubella), Maternal ingestion of Teratogens, Ototoxicity, Prematurity, Hypoxia, Kernicterus, Meningitis, Otitis media & NIHL. Nearly 10% of congenital deafness is caused due to infection. Avoidance of consanguineous marriages & Rubella vaccination may reduce the incidence in future.

The **etiology** of SHNL may vary from deafness caused due to inner ear anomalies - around 2-15% (Mondini's deformity) , absence of Cochlea or Syndromic deafness when associated with syndromes such as Ushers's, Alport & JLN syndrome. 30% of SHNL are syndromic in nature. Usher's syndrome characterized by progressive vision loss due to Retinitis pigmentosa & hearing loss is a tragic condition & is the most common anomaly found in India. Jervell and Lange Nielsen(JLN) syndrome characterized by cardiac conduction defect with hearing loss is also another common problem found in certain pockets of our population-Salem & North East to cite a few. Hearing loss is associated with at least 400 genetic conditions involving organs such as cranio facial, cervical, skeletal,integumentary,ocular,renal,neurologic pathways, thyroid, CVS & other metabolic conditions. The rest of 70% SHNL are non syndromic genetic conditions with 75-80% autosomal recessive,10-20% dominant & 2-3% X-linked modes of inheritance.

Dr. Mohan recalled his vast experiences with Cochlear Implanatation since 1996 at his institute. He assured that a congenitally deaf child can be made to hear completely through this technology. He gave an impressive account of the cases he has rehabilitated who have undergone normal schooling & are pursuing higher studies in the most coveted institutions in the country. Rigorous rehabilitation post transplant is very essential for these children for total success he added. Cochlear implant yields best when performed by 3 years of age. Even a 6 months delay will not do good based on the Surgeon's experience. The reason may be that the neural plasticity of the brain for language acquisition is at its best during this period. Hence early diagnosis & intervention through transplants facilitate language acquisition, social& better communication skills.

In the past children with profound SHNL, unresponsive to amplification hearing aids had to cope by lip reading or learning sign language. But this was not enough. They need to be communicative to cope with the fast developing modern world.

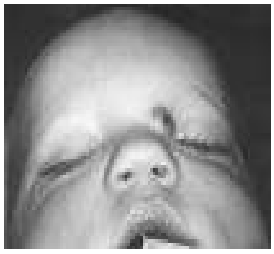
Introduction of new diagnostic treatment modalities has revolutionized the management of congenital deafness. The emphasis is now on early diagnosis and management. Newer investigational tools such as Oto Acoustic Emissions, BERA, Auditory Steady State Response, Middle Latency Response, and imaging modalities have helped diagnose and pinpoint the level of lesion along the auditory pathway, even in neonates and infants.

Bionic Ear(Cochlear Implant) is one of the most significant innovations of the last century in the field of Neuro Otology. It is a system of electrode array surgically implanted into the cochlea. An external device collects the sound, processes it and stimulates the implanted electrode by codified radio frequency messages. The cochlea like a piano when vibrated conducts sounds through its hair cells to cochlear nerves & the sounds are heard. When the cochlea is impaired due to absence of hair cells, the implant recovers the system of hearing by directly conducting the sounds to the nerves. Cochear implant is the only device that can sustain one's life time without needing replacement. It stays life long within the body without getting corroded!

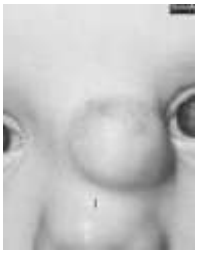
Cochlear implants - The cochlea is adult sized at birth

Cochlea itself may be absent in 1% of the cases. Auditory brainstem implants (ABI) are indicated for hearing loss due to bilateral absent cochlea and cochlear neves (Michel's deformity). The ABI stimulates the cochelar nucleaus directly thereby restoring audiotry sensation.

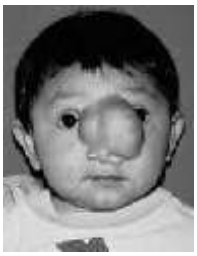
Talking of the Congenital Nasal Anomalies he said, the incidence of **nasal masses** such as Dermoid sinuses and Cysts, Gliomas & Encephaloceles is said to be 1:20,000 to 1:40,000 births.All three have potential intracranial connections & may present as a mass on nasal dorsum or as intranasal mass. Any unilateral nasal mass in a child should be evaluated for a congenital midline mass. Biopsy can lead to meningitis and CSF leak. Treatment is surgical excision with repair of the skull base.



Dermoid



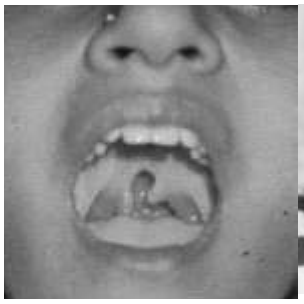
Gliom



Encephalocele

Congenital Nasal Haemangioma though uncommon can be distressing for the affected to see a nasal mass as big a potato & it needs to be excised. This is easily done with the excellent Fiber Laserization technique available today. The lesion is imploded & vapourized using this technology.

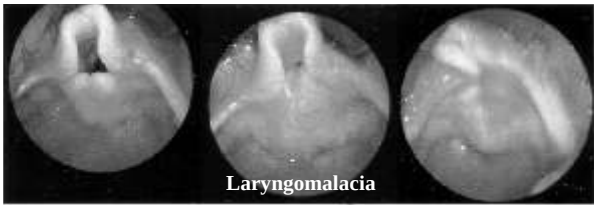
Congenital Choanal Atresia is an anomaly of the anterior skull base characterized by closure of one or both posterior nasal cavities. It occurs in 1/ 7000 to 8000 live births. Bilateral choanal atresia causes respiratory distress at birth. Unilateral lesions may go undiagnosed until the child presents with persistent unilateral nasal discharge. Patients with bilateral choanal atresia present with cyclic cyanosis relieved by crying. Diagnosis is by passing a small catheter through the nose into the nasopharynx, nasal endoscopy and CT, which is the investigation of choice. Control of airway followed by surgical excision is required.



Cleft palate is a condition in which the two plates of the skull that form the hard palate are not completely joined. The soft palate in these cases cleft as well. In most cases, cleft lip is also present. Cleft lips or palates occur in one in 600 - 800 births. Cleft palate can be isolated or be part of a syndrome. Within the first 2 - 3 months after birth, surgery is performed to close the cleft lip. Cleft palate surgery is usually performed between 6 and 12 months.

Congenital Laryngeal Anomalies can be grouped under Supraglottic, Glottic & Subglottic anomalies. The clinical manifestations of these would be Respiratory obstruction 1)Stridor 2)Weak cry 3)Dyspnea 4)Tachypnea 5)Aspiration 6)Cyanosis & 7)Sudden death.

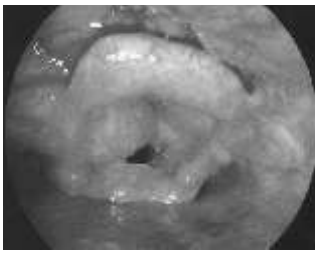
Laryngomalacia constitutes about 60% of the anomaly of the Larynx.



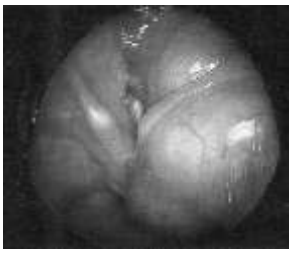
Laryngomalacia

Abnormal flaccidity of supra-laryngeal tissues is a temporary physiologic dysfunction that resolves with growth. Most important features include variable inspiratory stridor, signs of intermittent upper airway obstruction, normal cry and normal general health and development. The diagnosis is confirmed by direct endoscopic examination during respiration and exclusion of associated abnormalities in the tracheo bronchial tree. Parents must be reassured that this is a benign, self-limiting condition and that most cases resolve spontaneously within 12-24 months. Rarely, surgical procedures eg. Laserization of aryepiglotic folds are required.

Laryngomalacia due to Supragolttic Saccular cysts can be easily opened up & resolved. In the same way Supraglottic Haemangioma can be Laserized. These are easy & simple procedures.



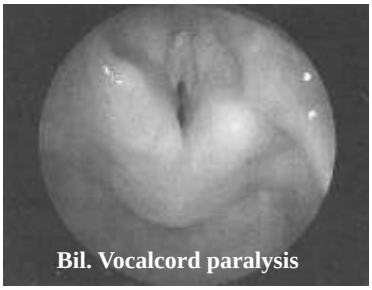
Supraglottic Saccular cysts



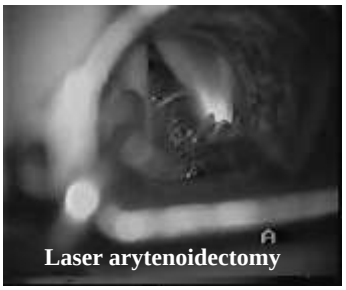
Supraglottic hemangioma

Laryngeal webs comprise of the **Glottic anomaly** which is caused due to failure of recanalization of larynx. Vocal cords are fused in this condition. If there is total atresia, the child will be born dead. There is a chance for the neonatologist to forcibly pierce open the membrane by intubating the child immediately at birth & thus safe the child. 75% of the web is found at the glottic level. Usually it involves the anterior 1/2 - 2/3rd of the glottis. The web can be divided endoscopically using scissors, knife or laser and external laryngofissure approach with placement of a stent may be used in difficult cases.

Congenital vocal cord paralysis is the second most common cause of weak cry / stridor . It typically presents within the first month of life and constitutes 6 - 13% with stidor. It may be unilateral / bilateral. Causes include neurologic disease in the brain, eg. Arnold Chiari malformation, cerebral palsy, hydrocephalus, hypoxic encephalopathy, intracranial space occupying lesions or cardiac problems. In most cases , the cause remains unknown.



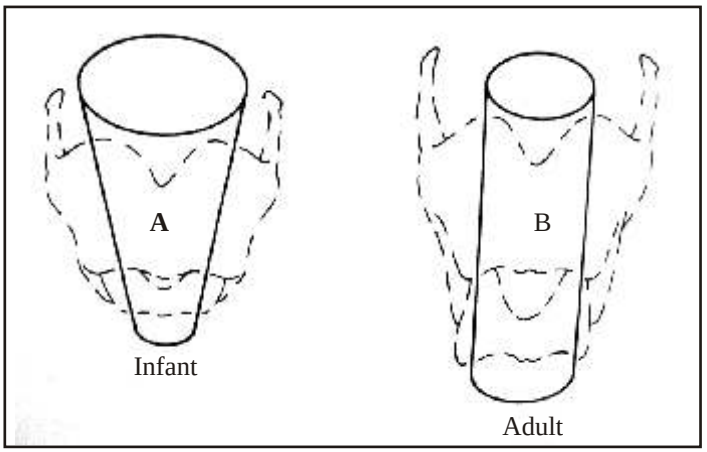
Bil. Vocalcord paralysis



Laser arytenoidectomy

Subglottic anomalies include **Subglottic Hamangiomas** which may be associated with cutaneous involvement (50%). Hemangiomas may be present anywhere in the head and neck. The patient may have Sturge - Weber syndrome. Airway obstruction may occur with hemangiomas in the subglottis and usually presents within the first 6 months of life. The classic appearance is of a pink or bluish smooth sessile mass. They usually regress by 5 - 8years of age. The recommended treatment is steroids and laserization.

Congenital subglottic stenosis is another common condition in which the laryngeal airway is narrowed due to failure of the laryngeal lumen to recanalise. It is <4.0mm in size and results in difficulty in breathing. After endoscopic laser excision, a stent may be used for a period 3 - 6months to maintain the patency of the operated area. External surgical procedures may have to be employed.



The narrowest portion of the infant's airway is the subglottis. Circumferential mucosal edema of 1 mm in the infant larynx narrows the subglottic space by > 60%

Congenital tracheal stenosis is a rare but serious anomaly & may be associated with anomalies of esophagus, CVS, RS and skeleton. Surgical options are dilatation, laser treatment, open repair & placement of stent. **Tracheomalacia** is weakness of the tracheal wall resulting in marked exaggeration of movement with respiration. It may be due to a congenital deformity of tracheal rings or secondary to external compression of the trachea by vascular anomalies or after surgical repair of tracheo-esophageal fistula.

While concluding his lecture Dr.Mohan Kameswaran said that congenital ENT problems constitute a significant proportion of otolaryngological ailments. They may be very challenging to the ENT surgeons but majority of them can be managed well with the advancements in ENT surgery. Early diagnosis & management of these disorders is essential and a team approach is often required in their successful management.

DISCUSSION

1) Can the laryngeal web recur again after surgery ?

Yes, it can recur in 1/4th of the children in whom laryngeal web has been excised. But when it recurs its size may not be as big and the child can have functional speech if not anything finer as the ability to sing! The surgeon added that Phonic implants are under research but Larynx is a more complicated part to deal with.

2) If majority of Down children have hearing loss, how do they develop a fascination for music?

Down children mostly have conductive hearing loss. If we are proactive by screening them early, this could be averted. They can be exposed to music to develop a liking.

3) Do all Haemangiomas need intervention?

Haemangiomas if not giving functional problems as breathing obstruction, need not be intervened. It is also possible to mange them medically using the new age drugs available which are effective.

NIAAMS

Screening is an essential part of preventive care. Screening program should have strict quality control and periodic audit in order to minimise false positive rates. All persons doing screening should be part of a "Screening program" in which all the stake holders participate for the excellent benefit of the patients. The NIAAMS (National Initiative for Anueuplodiy Anomaly for Metabolic Screening) project is a step in this direction. We request you to enroll in the NIAMMS network. For details log on to www.mediscansystems.org

Podium for Proactive members

BDRI welcomes writeup of interesting case presentations on Birth defects and their management from members for publishing in the forthcoming issues of "BDR News" Articles may be emailed to bdrichennai@gmail.com or hardcopies / CD may be mailed to our address

Happy & Prosperous New year 2010

To all the members of BDRI & FOGSI BDR

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