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MEDICAL INSIGHTS

Case-Based Discussions

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EDITION-4

The Complete Healthcare Experience for Women and Children

Message From The Editor

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Dear friends,

In the previous edition, we have discussed the various steps involved in evidence-based practice. The steps involved include:

1. Asking a question
2. Finding information/evidence to answer question
3. Critically appraise the information/evidence
4. Integrate appraised evidence with own clinical expertise and patient's preferences
5. Evaluating our effectiveness and efficiency in executing Steps 1-4 and seeking ways to improve them

In the previous edition, we have discussed about converting the information we need into an answerable question. Once we identify the clinical question, the next step is to search the available literature for evidence.

First comes the question: where do we search for evidence? Textbooks give knowledge about various conditions but may not contain the latest evidence. Current evidence can be obtained from recent journals and online search engines. Some of the useful websites to search for clinical evidence are summarized in the table below.

Website	Address
BMJ updates plus	http://plus.mcmaster.ca/EvidenceUpdates/
Sumsearch	www.sumsearch.uthscsa.edu/
TRIPdatabase	www.tripdatabasebase.com
Cochrane Library	http://www.cochrane.org/
DARE	http://www.crd.york.ac.uk/crdweb/
US national guidelines clearhouse	http://www.guideline.gov/
NICE	www.nice.org.uk
SIGN	www.sign.ac.uk
PubMed	www.pubmed.com
EMBASE	www.library.nhs.uk/

CONTENTS

CASE-1
AGGRESSIVE POSTERIOR RETINOPATHY OF PREMATURITY (APROP)
SCREEN IT RIGHT - SAVE THE SIGHT

A male baby was born at 32 weeks' gestation with a birth weight of 1240 g to a 25-year-old primi mother by LSCS (indication severe PIH). Increased resistance in the uterine arteries in USG Doppler was noted. Mother received one complete course of antenatal steroids. Baby cried at birth and was received in a plastic bag. Delayed cord clamping was done after 1 minute and was shifted to pre-warmed resuscitator. He developed respiratory distress soon after birth and was started on delivery room CPAP by T-piece resuscitator. Baby was shifted to NICU and was continued on CPAP support. Chest X Ray was suggestive of Respiratory distress syndrome. Baby was continued on CPAP support with maximum requirement of CPAP of 6 cm of H2O and 30% FiO2. Baby did not require surfactant replacement therapy and was weaned off from CPAP support by day 5 of life. Baby was initiated on minimal enteral nutrition after stabilization but developed abdominal distension and vomiting at 24 hours of life. Baby was kept nil per oral and was continued on total parenteral nutrition. He was initiated on iv antibiotics considering the possibility of sepsis which was stopped after 48 hours after the blood culture sample was reported sterile. Enteral feeding was reintroduced after 48 hours and gradually incremented to full feeds by day 9 of life, with a gradual transition to oral feeds with fortification by paladai. He received 3 weeks of caffeine therapy for apnea of prematurity. He was initiated on direct breastfeeding by 3 weeks of life and adequate postnatal weight gain was established.

Q1. Will you screen this baby for Retinopathy of Prematurity (ROP)?

Retinopathy of prematurity is a preventable but leading cause of blindness in premature infants. With improving survival of very-low birth weight infants in India, ROP is emerging as a significant problem with approximately 18,000 infants projected to become blind per year. In low- and middle-income countries, ROP affects babies with relatively higher birth weights and gestational age. Studies from India have reported ROP in 20-52% of screened neonates.

Indications:

- All preterm infants ≤ 34 weeks of gestational age
- All babies with birth weight < 2000 g
- Gestational age between 34 weeks and 36 weeks but with risk factors such as
    - Cardiorespiratory support
    - Prolonged oxygen therapy
    - Respiratory distress syndrome
    - Chronic lung disease
    - Fetal hemorrhage
    - Blood transfusion
    - Neonatal sepsis
    - Exchange transfusion
    - Intraventricular hemorrhage
    - Apnea
    - Poor postnatal weight gain

All preterm infants ≤34 weeks of gestation or birth weight <2000 g or gestation age between 34 and weeks with risk factor must be screened for ROP.

Q2: When to screen?

First screen at 4 weeks after birth.

There are no definite guidelines for screening at-risk APROP cases. The Royal College of Ophthalmologists guidelines suggest early screening at 30–31 weeks postmenstrual age (PMA) for infants born at <27 weeks GA, perhaps to detect APROP early. Similarly, the Indian guidelines recommend screening of preterm infants born <28 weeks or <1200 g earlier than usual (within 2–3 weeks rather than at 4 weeks) to detect APROP.

Follow-up examinations are recommended by the screening ophthalmologist based on retinal findings.

First screen should be usually at 4 weeks of life. However, screen within 2-3 weeks in preterm infants born at <28 weeks or <1200 g to detect APROP.

Case continued: ROP screening was done on day 21 of life which showed both eyes having APROP.

Q3: What is APROP?

AP-ROP is a rapidly progressing, severe form of ROP, which if untreated, usually progresses rapidly to stage 5 ROP. The characteristic features of this type of ROP include its posterior location, prominence of plus disease, and the ill-defined nature of the retinopathy. This may not have the classical ridge or extraretinal fibrovascular proliferation, but rather have innocuous looking retina and tortuous vessels forming arcades. This type of ROP is likely to get missed by inexperienced examiners. Observed most in Zone I, it may also occur in posterior Zone II. The iris may have prominent, persistent tunica vasculosa lentis (TVL) leading to pupillary rigidity and poor pupillary dilatation in the affected eyes. If dense, TVL may also obscure the retinal view. Vitreous haze is another important clinical feature of APROP but may even precede the development of APROP. The neovascularization is clinically less evident as the growth of abnormal vessels is along the retinal surface (flat neovascularization) instead of into the vitreous cavity. Less often the neovascularization may be brushfire like and grows into the vitreous cavity. The friable neovascular tissue tends to bleed, and it is common to find preretinal and vitreous hemorrhage in such cases. If not treated in time, the extensive flat neovascularization may progress to partial or total tractional retinal detachment (TRD) within a few days. The uncommon presentations include small zone I disease, a hybrid disease with additional ridge tissue, and APROP in bigger babies with birth weight greater than 1500 g.

APROP does not follow the usual stage progression as in classical ROP and can be easily missed by inexperienced examiner. If not treated in time, may progress to partial or total tractional retinal detachment within a few days.

Q4: What are the risk factors of APROP?

APROP cases often occur in premature babies with significant other co-morbidities. Dysregulated oxygen supplementation due to lack of oxygen

saturation monitors and unavailability of oxygen blenders is a significant risk factor for APROP. The independent risk factors reported for the development of APROP include extreme prematurity, thrombocytopenia, multiple infectious episodes, intrauterine growth retardation, and the presence of chorioamnionitis. The incidence of ROP in Indian settings is reported to range from 24% to 47%. The incidence rates of APROP are higher as compared to other countries which is around 4–5%.

Apart from dysregulated oxygen supplementation,extreme prematurity, thrombocytopenia, multiple infectious episodes, IUGR and chorioamnionitis are other independent risk factors. Screen the neonate for APROP within 2-3 weeks with above mentioned risk factors.

Q5: What is the role of fundus fluorescein angiography (FFA)?

APROP presentation is very atypical with an indistinct vascular–avascular junction, large vascular shunting loops enclosing capillary nonperfusion areas, and flat neovascularization along the retina, which may not be visible otherwise. The most significant advantage of FFA over color fundus imaging is that it aids in the better delineation of the capillary nonperfusion areas within the vascular loops. The apparently quiet junction on clinical examination may have angiographic evidence of neovascularization which leaks fluorescein profusely. The popcorn lesions present posterior to the junction are better appreciated on FFA as hyperfluorescent lesions.

Fundus fluorescein angiography may be considered for better delineation of APROP.

Q6: What are the treatment modalities for APROP?

- Laser photocoagulation
- Intravitreal injection of anti-VEGF drug
- Combination of Laser and anti-VEGF drug
- Vitrectomy

Laser photocoagulation: A favorable outcome in the form of complete disease regression with laser monotherapy ranges from 50–100% with most of the studies reporting it to be between 70 and 85%. This is less than the laser treatment success rates of above 90% in type 1 ROP cases. The progression of APROP can occur despite laser treatment leading to unfavorable outcomes such as peripheral TRD (stage 4a) and rarely stage 4b/stage 5/falciform fold formation. Various risk factors for unfavorable outcomes despite laser treatment in APROP are: GA < 29 weeks, presence of retinal hemorrhages, posterior zone I disease, extensive fibrovascular proliferation (>3 clock hours), need for multiple laser treatment, and development of new fibrovascular proliferation following laser. The more posterior the junction is, the lesser is the chance of a favorable outcome.

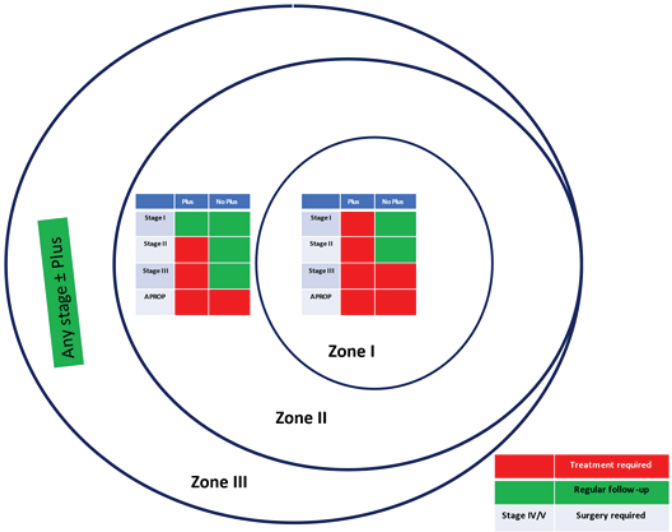
Intravitreal injection of anti-VEGF drug: There have been numerous reports/series of the use of anti-VEGF therapy in APROP as primary monotherapy, in combination with laser, as a rescue therapy after laser treatment failure, or as an adjunctive agent before vitrectomy. To date, the Food and Drug Administration, USA has not approved any of the anti-VEGF agents for the

treatment of ROP. The choice of agent in reviewed studies include Bevacizumab (BCZ) (commonly reported) and Ranibizumab (RBZ). There is no head-to-head trials comparing the efficacy of these drugs in APROP. Aflibercept (AFL) has also been used for treatment of ROP and has been reported to have the advantage of less frequent and more delayed recurrences than anti- VEGF agents, but there are no studies reporting outcomes with intravitreal AFL in APROP. BCZ is the commonly used off-label drug in a dosage of 0.625 mg (half the adult dosage) as used in the BEAT-ROP study. Recent research has shown that the vitreous cavity size-adjusted dose of BCZ in neonates might be 0.4 mg. The regression rates with a single injection in APROP ranges from 62.5% to 100. The risk factors for recurrence include lower birth weight and the presence of retinal hemorrhages. With re-treatment, a final favorable result is achieved in 78% to 100% of eyes. Advanced ROP (stage 4 or rarely stage 5) develops in a minority of the cases. The risk factors for progression of the disease to TRD despite treatment include a higher post-menstrual age at treatment and low neutrophil count. A recent historically controlled cohort study reported the incidence of retinal detachment to be around 10% in the laser treatment cohort as compared to 1% in anti-VEGF cohort. These results must be interpreted with caution due to possible biases in the study. Finally, a recent systematic review has indicated that anti-VEGF use in treatment of ROP in preterm neonates might be associated with poor long-term neurodevelopmental outcomes. With such conflicting evidence for its benefit-risk profile, its use in neonates warrants caution.

Combined treatment:

zThe combination treatment can be either simultaneous or sequential.

Laser photocoagulation has lesser treatment success in APROP as compared to Type 1 ROP. Anti-VEGF treatment has been shown to have better regression rate from observational studies specially if combined with Laser photocoagulation. However, the evidence is inconclusive.



Case continued: The neonate received intravitreal injection of anti-VEGF (BCZ) in both eyes on day 23 of life. The follow-up eye examination showed regression of ROP and hemorrhage and the baby did not require subsequent BCZ injection or laser photocoagulation.

Q7: Are there any long-term complications to these infants?

Treated ROP should be followed up till there are signs of complete resolution of the disease or vascularization of the retina or no signs of recurrence is adjudged. Eyes treated with intravitreal anti- VEGF need to be followed till

60 weeks post conceptional age or even longer as delayed recrudescence with anti-VEGF treatment is reported. All these babies with ROP should have yearly eye evaluation till 5 years of age.
Even if the anatomical outcomes are favorable, a long-term follow-up is necessary to detect refractory errors and strabismus. Late-onset rhegmatogenous retinal detachment has been reported after uneventful regression of APROP following laser treatment. The visual rehabilitation may be performed with spectacles or aphakic contact lenses in children undergoing lensectomy. Amblyopia treatment with patching should be provided to those with anisometropia or ametropic amblyopia. Failure of regression and disease reactivation are two significant limitations of anti-VEGF monotherapy, and these often require retreatment. Reactivation occurs once the effect of anti-VEGF drug present in the vitreous cavity wanes off. Reactivation commonly occurs between 40- and 52-weeks postconceptional age, i.e., between 2- and 10-weeks post injection. As compared to the classical type 1 ROP, APROP eyes have a five-fold increased risk of recurrence.

Refractory errors and associated strabismus, late onset retinal detachment are important problems in long term follow up after laser photocoagulation for APROP while failure of regression and reactivation in anti-VEGF group. Treated ROP should be followed up till there are signs of complete resolution of the disease or vascularization of the retina or no signs of recurrence is adjudged.

Q8: How to prevent ROP?

- **Antenatal steroids to mother with threatened preterm labor-**Though antenatal steroids have not been shown to reduce the risk of ROP, perhaps because it improves the survival rate of smaller babies who are at the highest risk of developing ROP. However, as it reduces the severity of prematurity related morbidities, they might reduce the occurrence of severe ROP.
- **Monitoring of oxygen delivery (Titrating FiO2 using a blender):** A large scale RCT (SUPPORT trial) indicated that maintaining low saturations (85% to 89%) compared to high saturations (91% to 95%) in preterm infants <28 weeks did not reduce composite outcome of death or severe ROP but it resulted in lower incidence of severe ROP but with higher mortality. Therefore, it is recommended that saturations in preterm neonates be maintained between 91% and 95%. Saturations should be monitored in preterm infants receiving oxygen therapy to prevent hyperoxia or hypoxia.

- **Judicious use of blood transfusion using restrictive thresholds**
- **Use of breast milk**
- **Early enteral nutrition and aggressive nutritional care**
- **Prevention and treatment of sepsis of caffeine**
- **Screening and treatment of ROP**

This case highlights the importance of screening for APROP at right time. The neonate did not receive dysregulated oxygen supplementation, however severe IUGR is considered as an important risk factor for APROP. Prevention is always better than cure. Primary prevention like implementation of best neonatal practices and simple measures like strict regulation of oxygen delivery can prevent development of APROP. The secondary and tertiary prevention strategies such as screening at right time and timely management would help in preventing blindness.

Take home messages:

- ROP is the leading cause of preventable blindness in preterm infants.
- Pediatrician in charge of the neonatal intensive care unit (NICU) is responsible for identifying infants to be screened, ensuring timely screening and follow-up.
- First screening should be at 30 days of life (at 2-3 weeks in <28 weeks and /or <1200 g or IUGR)
- In low/middle income countries, ROP affects babies with higher birth weights and gestational age.
- Although laser treatment remains the gold standard treatment for type 1 ROP, anti- VEGF agents are emerging as first-line treatment option for APROP. Their use is cautioned in view of recent evidence indicating poor neurodevelopmental outcomes.
- Annual eye evaluation of all babies with ROP till 5 years of age, whether treated or not is mandatory.

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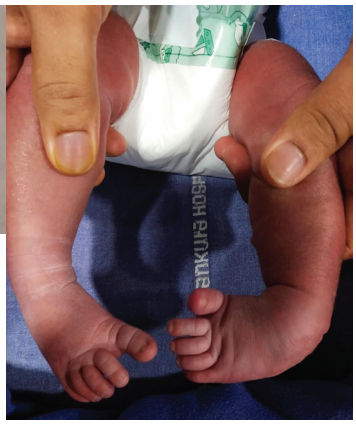
CASE-2
MANAGEMENT OF CLUB FOOT (CTEV) IN CHILDREN

INTRODUCTION

Congenital Talipes Equino Varus (CTEV) is one of the most common foot and ankle deformities in the new-born with occurrence rate of 1 in 1000 births, with slightly higher rates in the Indian subcontinent. The deformity with the foot bent inwards to around 90 degrees and in equinus posture resembles the bottom part of a golf club and hence the name.

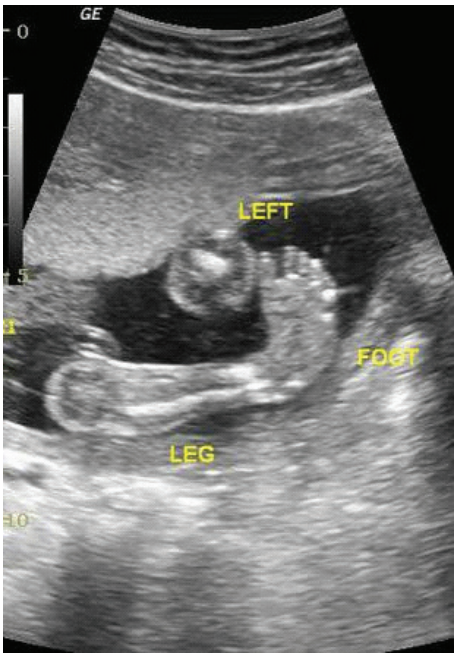


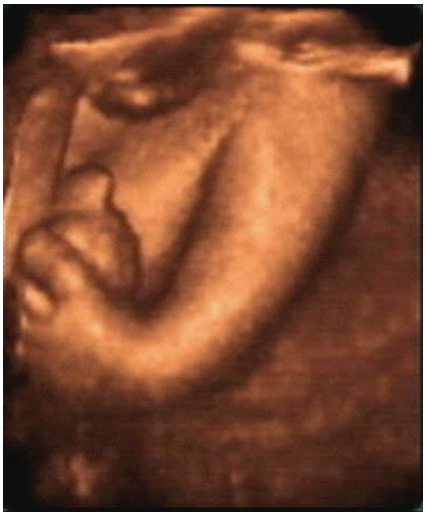
ETIOLOGY AND DIAGNOSIS

The exact cause of CTEV occurrence is unknown. The proposed theories include- packaging disorder wherein the mother has less liquor in womb, genetic predisposition and as a part of syndromic association. CTEV can therefore be idiopathic (unknown cause), neurogenic (caused by underlying neurological problem like spina bifida, cerebral palsy etc.) or syndromic (associated with syndromes such as arthrogryposis etc.)

Antenatal diagnosis:

Diagnosis of clubfoot is possible at around 20 weeks of gestation when screening for other deformities. However, around 1/5th of them might be false positive and require no intervention after delivery, the rest requiring treatment. Further rigidity and severity of deformity cannot be assessed antenatally. Syndromic CTEVs are harder to treat and have higher recurrence rates and poorer prognosis. At TIFFA scanning, if syndromic CTEV is noted with multiple deformities, parents are given an option of terminating the pregnancy by foetal medicine experts. However, for a simple idiopathic CTEV, termination of pregnancy is not advised as it can be completely treated.



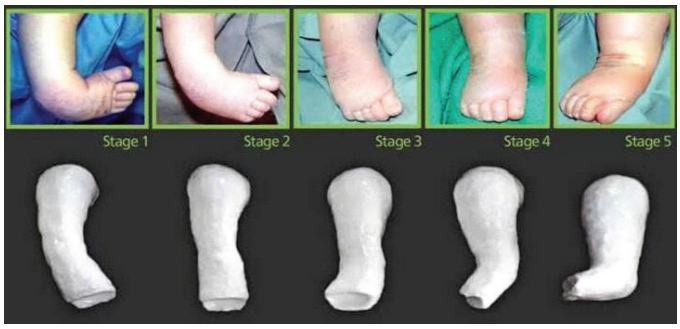


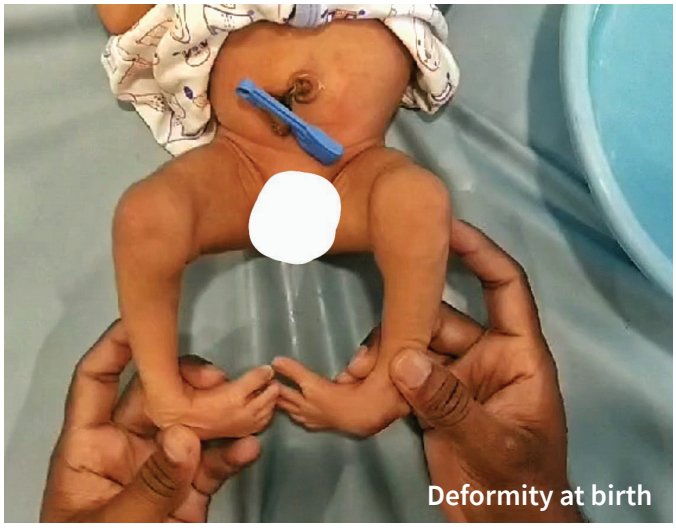
MANAGEMENT

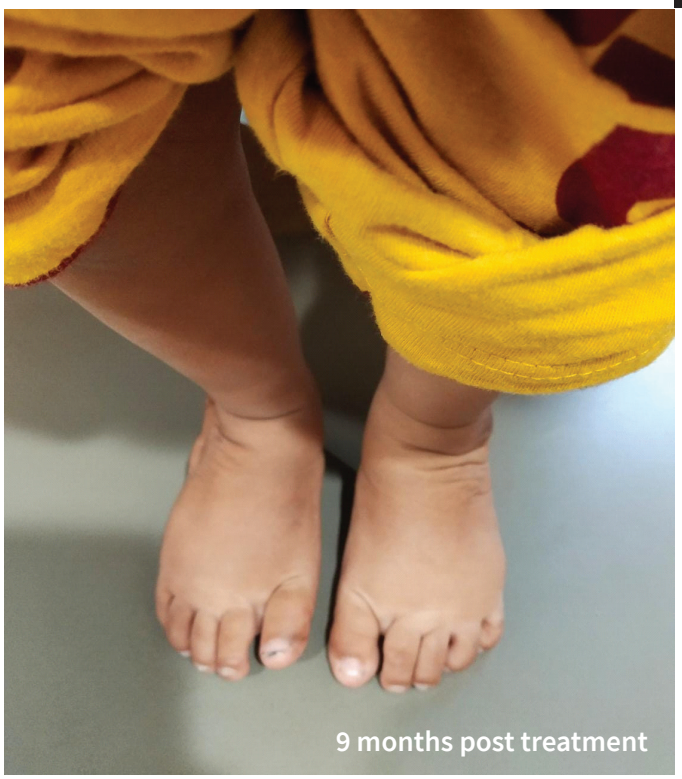
There are various modalities of treatments available for CTEV like Kite's technique, French tape technique etc., but the most extensively used method with best results is the Ponseti technique. The treatment consists of two phases: Ponseti serial casting and bracing.

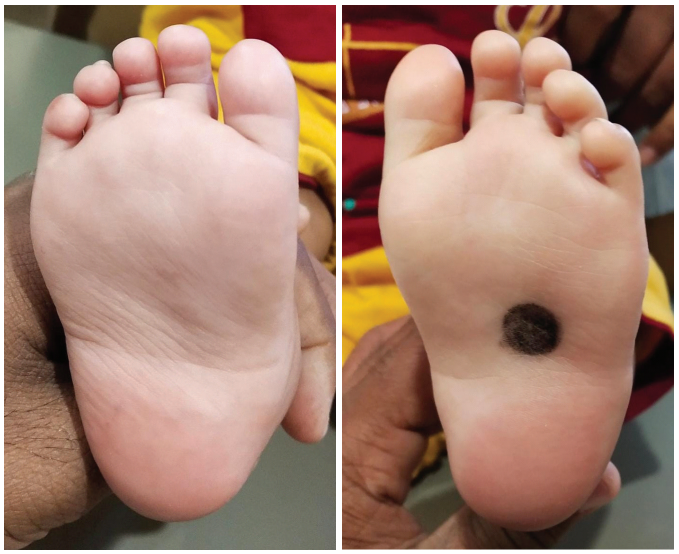
Ponseti technique:

This technique involves serial weekly manipulation and casting with plaster of Paris followed by tenotomy of the tendoachilles. Treatment is initiated within the first week of life when the baby's feet are supple. It takes 4-5 casts for complete correction of deformity. Tendoachilles tenotomy is then done under local anaesthesia as a day care procedure, with minimal incision scar, and no pain or blood loss. A final cast is placed after the procedure for a period of 3 weeks. Casts should be protected from soakage with water, urine etc. by constant wear of diapers.




Deformity at birth

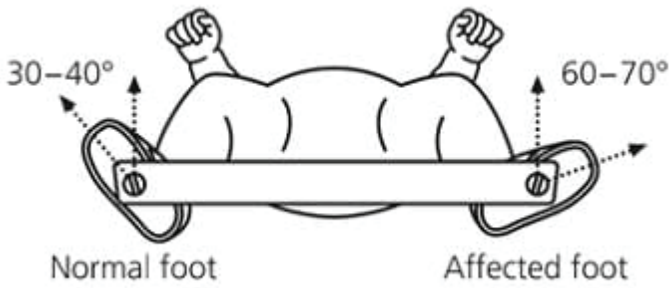

9 months post treatment



Bracing:

After removal of the final cast, Dennis brown splint is placed to maintain the correction. The braces are worn for 23 hours a day for initial 3 months thereafter reducing usage every 3 months to finally apply only at the time of sleep. Compliance to bracing is a major concern for every parent. Tips to improve compliance are rewarding the child for cooperation, bracing his/her favourite toys or relatives acting to be in brace with towel rolled around their feet etc. Children over age of 2 years learn to remove braces by themselves which can

be avoided with Velcro strapping or dynaplast taping. Correct usage of brace with complete heel touch to shoe, foot in abduction and dorsiflexion for up to 4 years can reduce recurrence rates to as low as 5%. Change of shoes every 3-4 months for upto 2 years and every 6 months for upto 5 years keeps the feet at comfort.



Physiotherapy:

A regimen of abduction, eversion and dorsiflexion every 2 hours, for 15 minutes each divided into 6-8 sessions keeps recurrence chances low.

RECURRENCE AND MANAGEMENT

Even after all the extensive efforts of treatment, bracing and exercise there is a chance of recurrence of deformity. This can present in various ways as heel not landing on floor, foot getting curved inwards, high arched foot and heel turning inwards. All these need to be addressed immediately and treatment initiated as soon as possible. Following up the baby every 3 months in first 2 years, every 4 months for the next 3 years is important to check for loss of flexibility and immediate diagnosis of recurrence.

The genetic memory in the leg and foot anatomy is the prime culprit for recurrence. Parents not following the brace and review protocol especially after the baby starts walking, adversely affects the outcome. Parents should not be falsely reassured that a walking child implies complete recovery. Recurrence in club feet is often treated with Ponseti technique again followed by procedures such as soft tissue releases, tibialis anterior transfer, osteotomies and JESS fixator system according to the deformity. Treatment plan is tailored to each patient and requires extensive clinical and radiological evaluation. Completion of recovery is indicated by absence of recurrence on follow up at 5 years of age (and 10 years age in a baby treated for recurrence).

SUMMARY

CTEV is one of the most common foot deformities. To ensure the best outcomes in CTEV, early diagnosis and initiation of treatment, proper bracing and physiotherapy, and regular follow up under the guidance of an experienced paediatric Orthopaedic surgeon is essential.

Let us join hands together to ensure that every baby has happy feet to dance through life.

Below are pictures of a child with recurrent CTEV treated at Ankura hospitals:

References:

1. Screening and management of retinopathy of prematurity. National Neonatology Forum CPG Guidelines 2020 using GRADE.

2. Rashtriya Bal SwasthyaKaryakram. c2019.https://rbsk.gov.in/RBSKLive/

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AS Rao Nagar	:	Beside ICICI Bank, AS Rao Nagar
Boduppal	:	Opp. Big Bazaar, Boduppal
Madinaguda	:	Opp. Maangalya Shopping Mall, Madinaguda
Balanagar	:	Opp. IDPL Colony, Adarsh Nagar, Balanagar
Mehdipatnam	:	Opp. Pillar No. 34, Rethibowli, Mehdipatnam
LB Nagar	:	Opp. Pillar No. 1643, Kothapet, LB Nagar
Khammam	:	Balaji Nagar, Khammam, Telangana
Tirupati	:	Korramenugunta, Renigunta Road, Tirupati

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