A RARE CASE OF MULTIPLE PTERYGIUM SYNDROME

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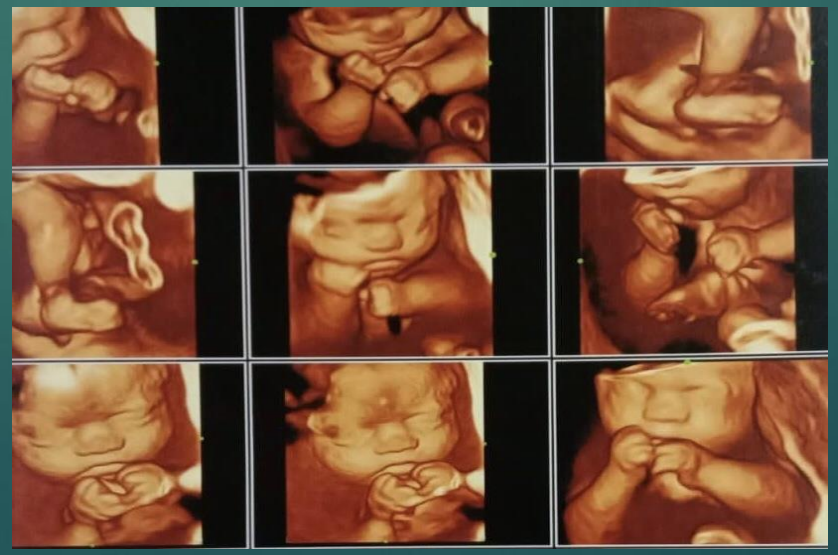
Case History

- A 9 day old neonate was bought to us with complaints of multiple contractures and dysmorphic features without any feeding difficulties .
- She is a term 2.7 kg female child born to a 26 yr old mother and 30 yr old father out of non consanguinous marriage via normal vaginal delivery cried immediately with no nicu admission.

Antenatal USG at 20 wk showing poly hydramnios with persistent mild degree of flexion deformity noted at knees and elbows ,persistent extension deformity noted at wrist joints,prominent renal pelvis of bilateral fetal kidneys.Possibility of club feet, Bilateral Rocker Bottom feet,With persistently hyperextended cervical spine,clenched hands.;imaging findings are s/o Arthrogryposis multiplex congenita.

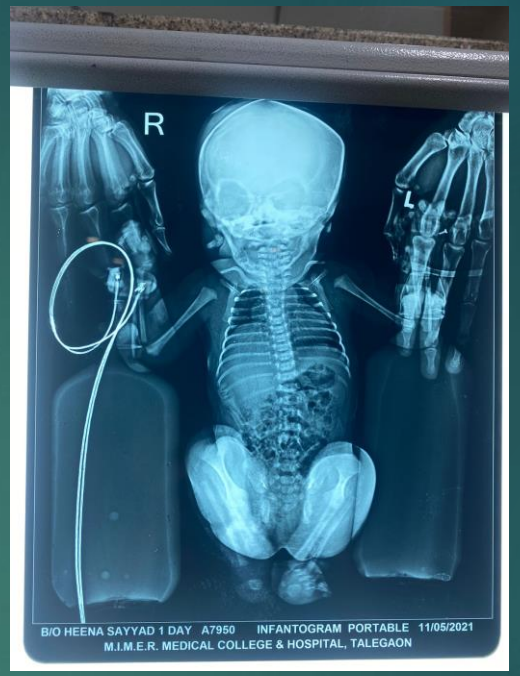


Clinical Examination

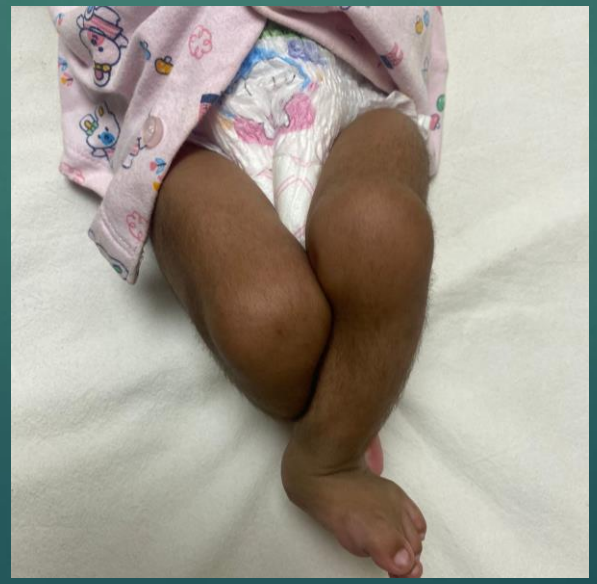
- On examination she had low set ears ,blue sclera , web neck,retrognathia ,high arched palate ,skin dryness present.
- The child has pterygium of bilateral axilla, antecubital fossa, wrist joints.
- There is bilateral flexion contracture of interphalyngeal and metacarpo phalyngeal joints with pterygium of fingers with camptodactyly.
- In lower limbs there was flexor contractures of both hips,knees ,ankles .
- There was marked rocker bottom heels with short halluces.

Child having multiple pterygium

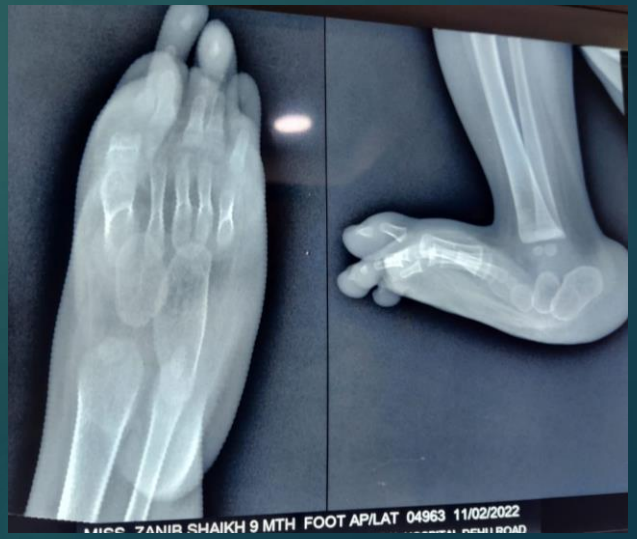
Pterygium at antecubital fossa and camptylodactyly i.e bent finger



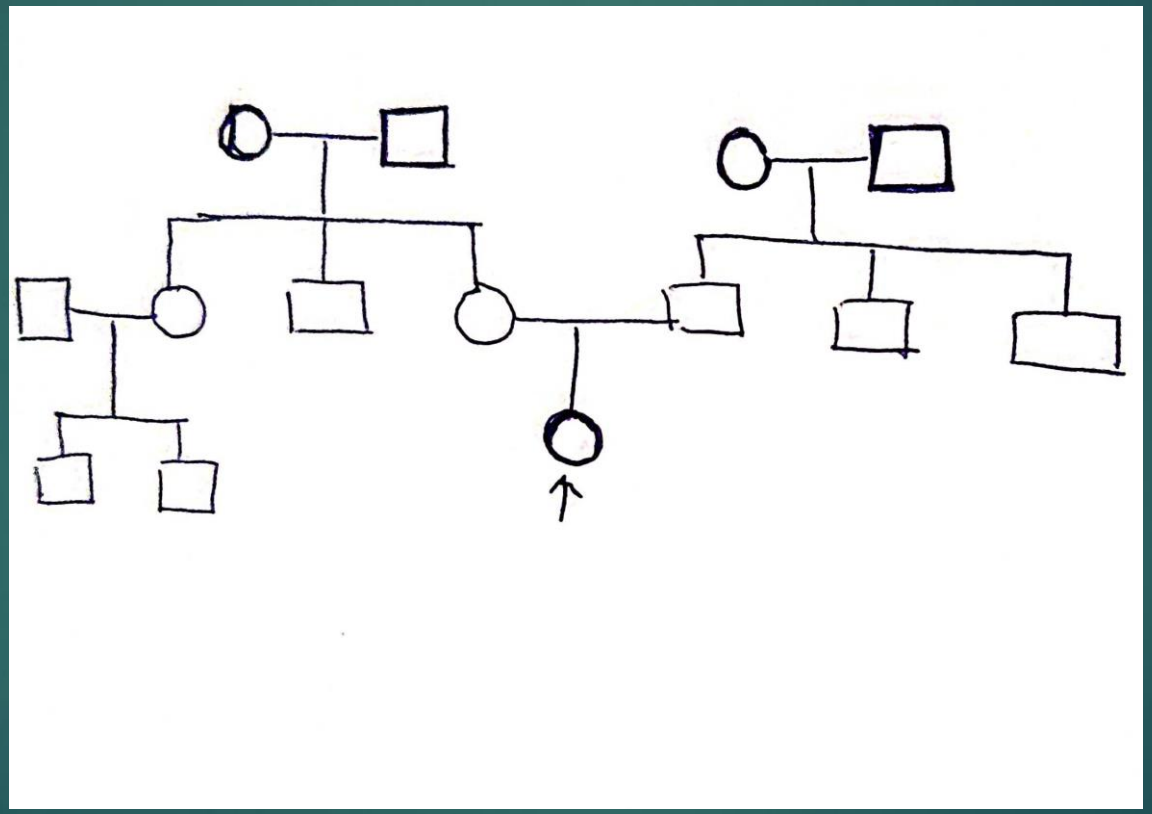
Pterygium at popliteal fossa



Rocker bottom foot



Pedigree chart



Systemic Examination

- Abdominal examination showed no organomegaly .
- Cardiovascular and respiratory examination were normal

- Differential diagnosis
  - Turner syndrome
  - Edward syndrome
  - Osteogenesis impfercta
  - Arthrogryposis multiplex congenita with its different types.
    - – Amyoplasia.
    - – Distal arthrogryposis.
    - – Pterygium syndromes such as LMPS and

Investigations

- Blood investigations were done and reports were normal
- OAE showing bilateral hair cells functioning abnormalities
- Abdominal ultrasonography showed no abnormalities
- 2decho showing small secundum asd with left to right shunt

GENETIC ANALYSIS

- **Karyotype** was normal
- **Whole exon sequencing**
- Gene: CHRNGN
- Location: Exon 7
- Inheritance: Autosomal Recessive
- Disorder : Multiple pterygium syndrome, lethal type(253290)

Case summary

- To summarise this is a case of 9 day old child who was bought to us with multiple contractures which were diagnosed to be present antenatally ,the child was vitally stable , investigations were done to rule out the causes of which karyotype was normal due to presence of multiple deformities whole exon sequencing was performed showing multiple pterygium syndrome .

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Original Article

Utilization of Whole Exome Sequencing in Lethal Form of Multiple Pterygium Syndrome: Identification of Mutations in Embryonal Subunit of Acetylcholine Receptor

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The Multiple Pterygium Syndrome (MPS)

- The multiple pterygium syndrome (MPS) –
- group of multiple congenital anomaly disorders recognizable by the presence of joint contractures (arthrogryposis) and skin webbing (pterygia) (Morgan et al., 2006).

- clinical subcategory of arthrogryposis multiplex congenita, the most severe form of fetal akinesias (Beecroft et al., 2018).

- prevalence of multiple pterygium syndrome is unknown but
- is thought to be <1 in 100 000.1 2
- There have been approximately 50 cases of this disorder reported in the medical literature.1
- Multiple pterygium syndrome has been found in Germany, France and England, and few cases - the Middle East and Africa.

Etiology

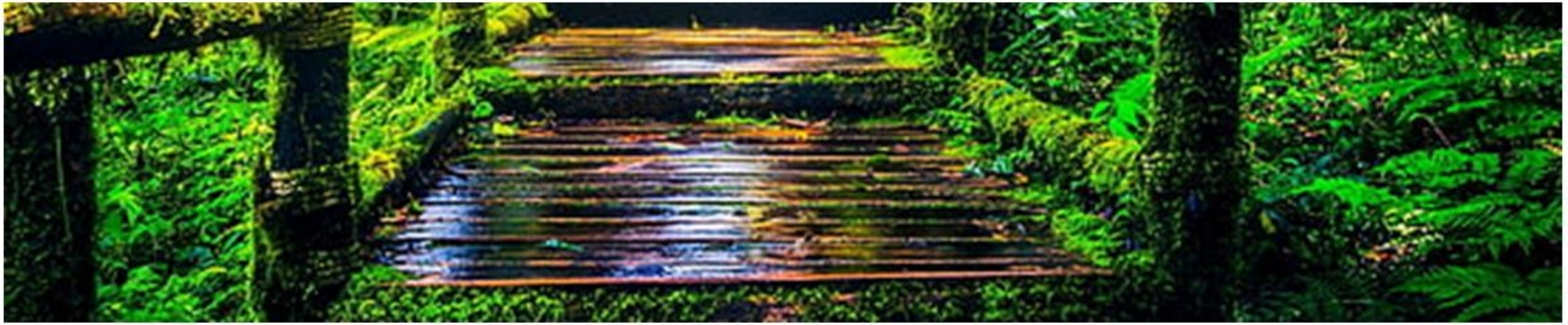
- Mutations in the **cholinergic receptor nicotinic gamma subunit** (CHRNG) gene cause autosomal recessive MPS.
- Encodes the gamma (γ) subunit of the acetylcholine receptor (AChR) of skeletal muscle (Hoffmann et al., 2006).
- The CHRNG gene7 provides instructions to make the gamma (γ) protein component (subunit) of the acetylcholine receptor (AChR) protein.

- AChR protein is found in the membrane of skeletal muscle cells and is critical for signalling between nerve and muscle cells.

- Signalling between these cells is necessary for movement.

- A lack of signalling between nerve and muscle cells leads to akinesia and pterygium before birth

Thank You



WES is a comprehensive and cost-effective approach to study heterogeneous diseases including MPS.

Useful for genetic counselingof high-risk families

preimplantation genetic diagnosis.

Sr No	Age /Sex	complaints	Microarray
1	Female /9 years	Short stature/ Vision problem/skeletal dysplasia	No clinically significant deletions, duplications or other chromosomal abnormalities were found.
2	4 years female	clinical features of down syndrome, developmental delay FTNVD/2.3kg/	FISH Down's syndrome
3	11 months male child	C/o GDD with PDA with Dysmorphism with hypospadias, C-section delivery,2.7 kg Flat occipit,	FISH: Negative for any abnormality as detected by probes for chromosome 13, 18, 21 and XY.
4	8yrs/M	delayed developmental milestone/ happy face with irrelevant smiling. decreased attention, mild intellectual disability.	FRAGILE X EXPANDED ALLELES DETECTION Microarray normal MS-MLPA -normal
5	9 years male,	Weight gain, difficulty in paying attention, not able to write fast Full term,lscs ivo oligohydramnios,3.4 kg,bciab, Depressed nasal bridge,short stature	MS-MLPA negative for Prader-Willi

Sr No	Age/ sex	Birth order/	Type of delivery	Clinical features	Investigations	Whole Exome Sequencing
1	4 years old M	non consanguineous	Birth weight 1200 g oligohydrimnious, NICU admission	failure to gain weight delayed development,triangular face low set ears,retrognathia,	USG cystitis, Echo normal	No pathogenic or likely pathogenic variant. However, variants of uncertain significance in RIPK1, KMT2C genes have been identified.
2	3 month/F	non consanguineous	polyhydramnios and intrauterine growth restriction	platycephaly ,low set ears,rocker bottom feet,hypertrichosis,blue sclera,bowing of legs. GDDlimb abnormalities,joint restriction,multiple jointcontractures,short stature dysmorphic	cong heart disease murmurplus, karyotyping normal,Echo ASD, USG head normal	CHRNG NM_005199.5 location on Exon 7 gene was detected on Whole exome sequencing .autosomal recessive A pathogenic variant in CHRNG gene,
3	Chaitanya Patil -					pathogenic variant in FUCA1 gene,

		consanguineous parents, 10 years Male		**episode of generalized tonic clonic seizures at 5th month of life along with fever** **Megalencephaly-polymicrogyriapolydactyly-hydrocephalus syndrome**	**abnormal slowing of activity suggestive of diffuse encephalopathy. Plasma leucine, valine and lactate were elevated. Urine analysis suggestive of 3 methyl glutaric aciduria ketosis, dicarboxylic aciduria, 3 hydroxy carboxylic aciduria.**	**Heterozygous** **Autosomal Dominant Likely Pathogenic PTCH1** **Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome-2 (MPPH2) is caused by heterozygous mutation in the AKT3 gene on chromosome 1q43-q44.**
		7 months Female	Birth history was uneventful	presented with developmental delay. There is no neck holding, no vocalisation, she has mongoloid spots and squint. Her tone is low, reflex +++, bilateral plantar reflex low.		No pathogenic or likely pathogenic variants causative of the reported phenotype were identified
		9 Years Female	non-consanguineous parents	presented with global developmental delay, wandering eyes, seizures and cerebellar signs.		MECP2 NM_Rett syndrome (312750) X-linked Dominant Pathogenic

Sr No	Age/ sex	Birth order/	Type of delivery	Clinical features	Investigations	Focussed Exome Sequencing
1	6 years male	first product of consanguineous marriage	Term/ LSCS NICU admission	GDD/hyperactivity/ behavioral issues/cognitive delay /	MRI : prominent VR spaces BERA normal and costellar syndrom/ Pallester Killion syndrome/3 M syndrome	a carrier of a pathogenic variant in the GNRHR gene.Hypogonadotropic hypogonadism Karyotype-9
2	Female	first product of non consanguineous marriage	Preterm LSCS 2kg history of Oligohydramnios	Global delay	Congenital heart disease ASD VSD MRI: Ventricular dilatation partial agenesis of carpus callosum delayed myelination	variants of uncertain significance in MYLK2, POLA1. carrier for a likely pathogenic variant in LIFR gene VanEschO Driscoll syndrome
3	8 years old male	third product of non consanguineous marriage	Term normal delivary	Seizures aggressive behavior, developmental delay	MRI -Prominent temporal horn of right ventricle flattening of hippocampus	
4	2 months old , female Jainaba	first product of consanguineous marriage	Full term NVDNicu admission	Erratic movement of rt hand and lower limbs, Abnormal facies,hepatomegaly	MRI Cerebral atrophyMetabolic seziures Newborn screening Fumarate hydrate deficiency	carrier of a pathogenic variant in HBB gene and a likely pathogenic variant in GALC gene.

Sr No	Age/ Sex	Birth order/	Type of delivery	Clinical features	Investigations	Focussed Exome Sequencing
5	2 years Male Manas Rane	second product of non consanguineous marriage	NICU admission feeding difficulty	global developmental delay, laryngeal cleft, hypertonia, seizures, facial dysmorphism, microcephaly, hypertrichosis and feeding difficulties.	MRI suggestive of perinatal hypoxic ischemic insult.EEG abnormal GCMS Negative Microarray normal.	No pathogenic or likely pathogenic variant, variants of uncertain significance in DDHD2, GLDC and ATN1 genes have been identified. a carrier of a pathogenic variant in AKR1D1 gene.
6	4 years male Krishna			global developmental delay, left sided tonic-clonic seizures, status epilepticus, uprolling of eyes and seizures usually happens in sleep.		SCN5ANM_198056.3 c.3037C>A (p.Pro1013Thr) Exon 17 Heterozygous Brugada syndrome 1 (601144) Autosomal Dominant Uncertain Significance
7	5 yrs F Neelam	consanguineous parents,		global developmental delay, frequent falls, unable to walk or sit, unable to stand with support, episodes of seizures, focal seizures, delayed motor development, delayed language development, intellectual disability,ataxia		MED13 chr17:60106960T>C - Uncertain SignificanceAutosomal dominant autism spectrum disorder and attention deficit-hyperactivity disorder (ADHD).

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Conflict of interest
We declare no conflict of interest.

Key messages

- Early diagnosis, prevent unnecessary neurological or muscular testing
- Early supportive measures
- facilitate counselling for future pregnancy.
- Preimplantation genetic diagnosis if they choose to do so.
- Recessive pattern of inheritance for this disorder, more cases in consanguineous marriage.

Case report Lethal multiple pterygium syndrome Farzeen Shuaib Mohtisham, 1,2 Adel Sallam,1,2 Aiman Shawli2,3Mohtisham FS, et al. BMJ Case Rep 2019;12:e229045. doi:10.1136/bcr-2018-229045


Thank you