UNRAVELLING THE DIAGNOSTIC DILEMMA - Case series of radiologically diagnosed pontocerebellar hypoplasia.

Ami Shah[1,4], Shilpa Kulkarni[2], Foram Gala[3], Snehal Mallakmir[4]

1. Department of Genetics, B J Wadia hospital for children, Mumbai, India. 2. Department of Neurosciences, B J Wadia hospital for children, Mumbai, India. 3. Department of Radiology and Imaging, B J Wadia hospital for children, Mumbai, India.
4. Department of Genetics, Nanavati MAX Super Specialty Hospital, Mumbai India.

Contact : Ami Shah – drami.rajesh.shah@gmail.com

Wadia Hospitals

597

ICNC 2022 – 17th INTERNATIONAL CHILD NEUROLOGY CONGRESS

PONTOCEREBELLAR HYPOPLASIA (PCH) [1]

Umbrella term for a heterogenous group of disorders
Characterised by hypoplasia of Cerebellum + Pons
Prenatal onset , Progressive disorder
Generally early onset developmental delay with variable intellectual disability, tone abnormality, seizures, microcephaly and poor outcome
Genetically variable, usually autosomal recessive in inheritance
Previously used 'PCH' now has many differentials.

CASE SERIES

We did a retrospective analysis of patients with Antenatal and / or postnatal Clinical / Radiological / Genetic diagnoses of PCH seen from January 2021 – March 2022.

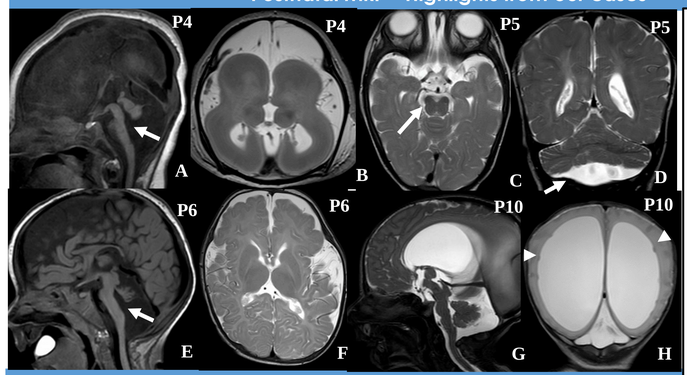
Time of suspicion	Antenatal	Postnatal
Number of patients	4	6
Family history	3	3
Clinical features		
Significant birth history	3	3
Dysmorphism	3	1
Microcephaly	2	3
Global developmental delay	-	5
Seizures	2	2
Tone abnormalities	3	4
Arthrogryposis	3	0
Ophthalmic abnormalities	0	2
Genetic Testing		
Sent	3	1
Positive	2	0
Outcome		
Alive	0	6
Abortion	1	0
Death (age)	3 – in 1st month	0

NEUROIMAGING

Remains the mainstay for diagnosis and etiological clues based on pattern recognition
Prenatal ultrasound is unreliable, MRI remains the modality of choice

	Antenatal suspected cases			
	P1 (elder sibling of P2)	P2	P3	P4
Antenatal	@ 30 wks microcephaly, reduced movements	@ 30 wks microcephaly, reduced movements, reduced Pontocerebellar volumes	@ 18.5 wks Increased nuchal fold Cerebellar hypoplasia, flexion at hip, knee, ankle joint, Bilateral clenched hands	@ 29 wks Enlarged cisterna magna, Vermis and cerebellum hypoplastic, Polyhydramnios
Postnatal	Skull Ultrasound B/L cerebral hemisphere band like thickening s/o ? Heterotopia	Postnatal Normal ultrasound	-	MRI (Fig 1. A,B) Bilateral micro lissencephaly Hypoplastic cc Abs basal ganglia and IC PCH

Postnatal MRI - Highlights from our cases



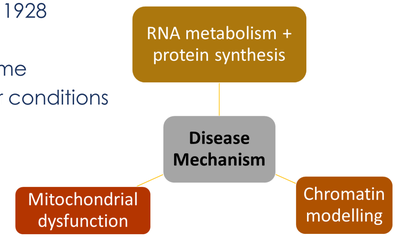
A, E : PCH
B : Microlissencephaly, absent basal ganglia + internal capsule
C: Figure of 8 appearance of midbrain on axial images.
D: Prominence of cisterna magna is seen.
F: Bilateral small globus pallidus nuclei. Delayed myelination
G: Aqueductal stenosis and
H: periventricular nodular heterotopia

Positive Genetic results in our cases

	Gene detected	Variant Classification	Diagnosis
P1,2 (Siblings)	COASY	Pathogenic, Novel	PCH 12
P3	NEB	Compound heterozygous, Uncertain significance	Arthrogryposis multiplex congenita 6

DISCUSSION[1,2]

First reported in 1917, clinical characteristic described in 1928
First classification came in 1993, now 13 types are listed
Phenotype – Genotype spectrum has expanded over time
Variable phenotype : Prenatal lethal → late onset milder conditions
Many unique clinical + radiological features defined
Molecular testing remains mainstay for diagnosis
Treatment remains supportive



Pathophysiology:

- Alteration of RNA metabolism/ protein translation is a common mechanism behind at least some of the PCH subtypes.
- Other mechanisms like Mitochondrial dysfunction and maintenance defects and Cellular function defects are also known

DIFFERENTIAL DIAGNOSIS – Why still a dilemma? [2]

The group included only cerebellar hypoplasia at onset Now also includes cerebellar atrophy

1. Expanding classification + limited information makes it difficult for clinicians
2. No standard measurements = variable imaging interpretation
3. Molecular testing may not end the diagnostic odyssey (variants of uncertain significance)

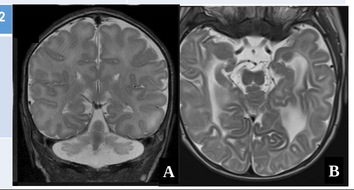
Pattern recognition approach - careful assessment of clinical + radiology aids in differentiating

Common differentials [2,3]

Congenital disorders of glycosylation	CASK – reltd disorders	Tubulin defects
Alpha dystroglycan reltd dystrophinopathies	Pediatric onset spinocerebellar ataxia	Extreme prematurity

Common imaging patterns pointing towards specific etiology[2]

Infratentorial anomalies	Non lobulated vermis Dragon fly pattern Brainstem grooves, kinking Cerebellar cortex HI, Cysts
Supratentorial anomalies	Agenesis of corpus callosum Simplified gyral pattern Hypomyelination Brain calcification
Pontine protuberance , cerebellar volume	



A: Dragon fly pattern in a case of PCH 2A[2]
B : figure 8" appearance of the lower mesencephalon in a case of PCH 9[2]

TAKE HOME MESSAGE

Have a pattern-based approach – using unique clinical + imaging features
Interpret molecular test with caution – Beware of uncertain variants + Phenotype genotype correlation
More collaborative research required for better understanding and for definitive treatment

References

1. van Dijk T, Baas F, Barth PG, et al. What's new in pontocerebellar hypoplasia? An update on genes and subtypes. Orphanet J Rare Dis. 2018 Jun 15;13(1):92. 2. Rüsch CT, Bölsterli BK, Kottke R, Steinfeld R, Boltshauser E. Pontocerebellar Hypoplasia: a Pattern Recognition Approach. Cerebellum. 2020 Aug;19(4):569-582. 3. Accogli A, Addour-Boudrahem N, Srour M. Diagnostic Approach to Cerebellar Hypoplasia. Cerebellum. 2021 Aug;20(4):631-658.