Clinico-radiological Profile of Children with Pontocerebellar Hypoplasia

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Aims and Objectives: Pontocerebellar hypoplasia (PCH) constitutes a heterogeneous group of neurodegenerative/neurodevelopmental disorder of pons and cerebellum with onset in prenatal period. This study aimed to discuss the clinical, radiological profile, and outcome of four infants with PCH attending our center.

Materials and Methods: Data of children with psychomotor retardation seen between January 2015 and December 2015 at neurodevelopmental clinic was retrieved. PCH was defined by clinical and radiological criteria. Clinical features included were delay in attainment of milestones in more than two developmental domains accompanied by severe microcephaly. Radiological evidence of cerebellar volume loss with hypoplasia of pons was included. Patient charts were reviewed for clinical features, neuroimaging, electroencephalography, and biochemical investigations including serum and cerebrospinal lactate. Molecular genetic testing for the common p.A307S mutation in TSEN54 of the cases and their parents were also analyzed.

Results: During this period, 101 children with psychomotor retardation were evaluated at our center. Of the 101, four children were with clinical and radiological evidence of PCH. In addition to psychomotor retardation and severe microcephaly, spasticity, bipyramidal signs, and epileptic spasms were universal in all four children. Three of the four children had optic atrophy and two had sensorineural hearing loss. Severe cerebellar hypoplasia with attenuated pons was seen in all four children. Two children had dragonfly appearance of cerebellum on coronal section. The commonest TSEN54 p.A307S mutation in children and their parents was not detected.

Conclusion: A heightened index of suspicion for PCH is merited in infants with progressive psychomotor retardation and severe microcephaly. Cerebellar hypoplasia with pontine attenuation forms the mainstay of diagnosis of PCH.

Keywords: Epileptic spasms, microcephaly, pontocerebellar hypoplasia

INTRODUCTION

Pontocerebellar hypoplasia (PCH) constitutes a heterogeneous group of neurodegenerative disorders of pons and cerebellum with onset in the prenatal period. PCH draws attention by its clinical features of severe microcephaly, profound global developmental delay, and the radiological hallmark of cerebellar and pontine hypoplasia. The presentation, however, is diverse ranging from lethal neonatal subtypes to milder variants who survive into adolescence. The disorder is further compounded by sparing of the pons in few cases. Advancements in genetic testing have identified at least 10 different subtypes of PCH, to date. Given the paucity of data on PCH from developing countries, this study aimed to discuss the clinical and radiological profile of four infants with PCH.

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Materials and Methods

This study is a retrospective review of children with a clinical-radiological diagnosis of PCH identified from the neurology clinic records over the period January 2015 to December 2015. During the study period, all infants with global developmental delay meeting the criteria for PCH were identified. PCH was defined by the following clinical and radiological criteria. Clinical features included the delay in attainment of milestones in more than two developmental domains accompanied by severe microcephaly and radiological evidence of cerebellar volume loss with hypoplasia of pons. Any child with occipitofrontal circumference of Z scores > –3 was taken as severe microcephalic. Children with a history suggestive of neonatal encephalopathy secondary to perinatal asphyxia, meningitis, or intracranial bleed were excluded. Children with associated malformations of cortical development on neuroimaging were excluded from the study. Patient charts were reviewed for clinical features, neuroimaging, electroencephalography, and biochemical investigations including serum and cerebrospinal lactate. Molecular genetic testing for the common p.A307S mutation in the TSEN54 gene of the cases and their parents were done. These children were followed up for at least 1 year.

Results

During the study period, a total of 436 children were enrolled in our Pediatric Neurology clinic. Of the total 101 children worked up for global developmental delay, four children fulfilled clinical and radiological criteria of PCH [Table 1]. Molecular genetic testing for the commonest TSEN54 p.A307S mutation in the children and their parents was done and no mutation was detected. Bipyramidal signs and epileptic spasms

| Case 1 | Case 2 | Case 3 | Case 4* |
|---|---|---|---|
| Age, sex | 3 years, F | 8 months, F | 2.5 years, F | 1.5 years, M |
| Consanguinity | Nil | Nil | III degree | III degree |
| Term/preterm | Term | Term | Term | Term |
| Antenatal | Polyhydramnios | – | Yes | Yes | – |
| Fetal distress | – | Yes | – | – |
| Congenital contractures | Present | – | – | – |
| Postnatal | Spasticity | Yes | Yes | Yes | Yes |
| Dystonia | Yes | No | Yes | Yes |
| Hypotonia | No | No | No | No |
| Epileptic spasms | Yes | Yes | Yes | Yes |
| Microcephaly | Yes | Yes | Yes | Yes |
| Visual failure | Yes | Yes | No | Yes |
| Optic atrophy | Yes | Yes | No | Yes |
| Retinal abnormalities | No | No | No | No |
| Deafness | Yes | No | No | Yes |
| Exaggerated startle | No | Yes | No | No |
| Genital abnormalities | No | No | No | No |
| Scoliosis | Yes | No | No | No |
| Family history | No | No | No | No |
| Others | Hip dislocation | Long fingers | – | – |
| Neuroimaging | Ventral pons flattening | Yes | Yes | Yes |
| Cerebellar abnormalities | Yes | Yes | Yes | Yes |
| Vermis hypoplasia | Yes | Yes | Yes | No |
| Hypoplastic hemispheres | Yes | Yes | Yes | Yes |
| Dragonfly appearance | Yes | Yes | No | No |
| Butterfly appearance | No | No | Yes | No |
| Cortical atrophy | No | Yes | No | Yes |
| Abnormal myelination | No | No | No | Yes |
| Follow-up | Age at last examination | 5 years | 2 years | 4 years | 2.5 years |
| Developmental age | 4–6 months | <2 months | 6–8 months | 6 months |

*Died because of intercurrent lower respiratory tract infection; none of the children had postnatal hypotonia, retinal or genital abnormalities; positive family history
were seen in all the affected children. Optic atrophy was seen in three of the four children. All children were started on neurorehabilitative measures and required adrenocorticotropic hormone therapy for epileptic spasms. Epileptic spasms were refractory in nature requiring more than three antiepileptic drugs for seizure control in all. Three children completed 2-year follow-up with persistent features of profound global developmental delay and one child (case four) succumbed to intercurrent respiratory illness.

**Discussion**

Following the first description in 1917, PCH has been increasingly recognized as significant cause of profound global developmental delay with progressive microcephaly. The spectrum of PCH has, thus, expanded to a total of 11 different subtypes, based on differences in the clinical and genetic profile; PCH type 2A is the commonest form and is caused by homozygosity for the p.A307S mutation in *TSEN54*. The distinctive clinical and genetic features of the 11 subtypes are summarized in Table 2.

There are currently 17 genes that are associated with PCH. Many of these genes have a role in RNA metabolism or protein translation. *TSEN54*, for instance, is one of the four subunits of the transfer-RNA splicing endonuclease complex (TSEN-complex). This complex is involved in the splicing of intron-containing pre-tRNAs. Mutations in *TSEN2*, *TSEN34*, and *TSEN15* are associated with PCH2B, PCH2C, and PCH2F, respectively, and occur very rarely. However, the exact pathogenesis of PCH 8 disorder is poorly understood and a singular pathway unifying all the genes responsible for PCH is lacking. The histopathological correlate is the loss of Purkinje cells with impaired foliation of the cerebellum and loss of pontine fibers as a secondary effect of the severe prenatal oncer cerebellar hypoplasia.

The shared clinical profiles of our cohort include severe microcephaly, seizures, pyramidal/extrapyramidal involvement, and poor psychomotor development. In addition, the clinical continuum also encompassed polyhydramnios (2/4), visual inattention (3/4), and sensorineural deafness (2/4). This clinical phenotype is similar to the largest series of 169 children of PCH published by Namavar et al. However, the children in our cohort were all born term, unlike Namavar et al., where prematurity was seen in 24% of children. Furthermore, Kayserili et al. reported on four children

| Subtype | OMIM | Distinctive feature | Gene |
|---------|------|---------------------|------|
| PCH 1   | 607596 | Anterior horn cell degeneration | *PCH1A*, *VRK1*, *PC1B*, *EXOSC3*, *PCH1C*, *EXOSC8*, *PCH1D*, *SLC25A46* |
| PCH 2   | 277470 | Dystonia, chorea, impaired swallowing | *PCH2A-TSEN54* (p.A307S mutation) *PCH2B-TSEN2* *PCH2C-TSEN34* *PCH2D-SEPSECS* *PCH2E-VPS53* *PCH2F-TSEN15* *PCLO* *TSEN54* |
| PCH 3   | 608027 | Optic atrophy | *PCLO* |
| PCH 4   | 225753 | Hypertonia, severe clonus, polyhydramnios, contractures, primary hypoventilation | Compound heterozygosity for the p.A307S mutation with on the other allele a splice site or nonsense mutation. *TSEN54* |
| PCH 5   | 610204 | Similar as PCH4 | |
| PCH 6   | 611523 | Encephalopathy; elevated CSF lactate, apnea | *RARS2* |
| PCH 7   | 614969 | Disorders of sex development | *TOEI* |
| PCH 8   | 614961 | No progression | *CHMP1A* |
| PCH 9   | 615809 | Figure of eight brainstem | *AMPD2* |
| PCH 10  | 615803 | Central and peripheral nervous system involvement | *CLP1* |
| PCH11   | 617695 | Nonprogressive PCH | *TBC1D23* |
The magnetic resonance imaging (MRI) signature of PCH is the variable degree of cerebellar hypoplasia with pontine involvement.[5] On the basis of the vermis and hemispheric involvement, Namavar et al. suggested a significant association between the common TSEN54 mutation and dragonfly-like cerebellar hemispheres. Two children in our cohort showed this dragonfly appearance with negative genetic results [Figure 1]. In addition, abnormal myelination and cortical atrophy were the other associated features in our cohort.

Of the 10 subtypes, TSEN54 mutation for PCH type 2 is the most common type.[7] In our case series, gene sequencing in the trios (index child and parents) did not identify the TSEN54 p.A307S mutation. Lack of genetic identification could be because of several reasons. Genetic testing was done only for the commonest TSEN54 p.A307S. The entire TSEN54 gene sequencing was not possible because of financial constraints. Moreover, absence of this particular mutation may suggest the possible role of other novel mutations or a different gene in our cohort. Furthermore, in the largest series of 169 children, genetic testing detected mutations in only 63% highlighting the unidentified genetic mutations of this phenotype.

Congenital disorders of glycosylation type 1a, lissencephaly with cerebellar hypoplasia, dandy walker syndrome, congenital muscular dystrophy, serine biosynthesis, and CASK gene defects are close differentials for PCH and have to be evaluated, especially in unsolved cases. The blood acylcarnitines on tandem mass spectrometry and urine organic acids on gas chromatography–mass spectrometry, in our cohort, were normal.

The treatment of PCH is symptomatic and includes nutritional rehabilitation, management of seizures, respiratory support, and physiotherapy. The identification of causative mutations facilitates counseling of the parents regarding the recurrence risk and offering of prenatal testing.

In conclusion, a heightened index of suspicion for PCH is merited in infants with progressive psychomotor retardation and severe microcephaly. Cerebellar hypoplasia with pontine attenuation forms the mainstay of diagnosis. The advances in genetic diagnostics offer hope for genetic confirmation and thereby creating the possibility of prenatal genetic testing in families with a high recurrence risk.

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Conflicts of interest
There are no conflicts of interest.

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