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Pontocerebellar Hypoplasia Type 6: A Rare Disorder in Two Siblings

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Abstract

Pontocerebellar hypoplasia type 6 (PCH-6) is a mitochondrial disease caused by mutations in the RARS2 gene. It is characterized by severe neurodevelopmental impairment, progressive microcephaly, seizure, cerebellar and pontine hypoplasia. We present a detailed description of two siblings with PCH-6. They had similar symptoms like developmental delay, seizure, and microcephaly. Neuroimaging abnormalities were found in both patient but finding typical for PCH-6 was only found in patient-1. Whole-exome sequencing confirmed that both siblings harbored the same compound heterozygous c.1A>G (p. Met1?) and c.574_575delinsTT (p. Glu192leu) variant in RARS2 gene. This case report highlights the clinical features, and diagnosis of PCH-6 in two siblings. A heightened index of suspicion for PCH-6 is merited in infants with developmental delay, intractable seizure, and microcephaly.

Keywords: Developmental delay, intractable seizure, microcephaly, pontocerebellar hypoplasia-6, RARS2

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Introduction:

Pontocerebellar hypoplasia (PCH) refers to a group of neurodegenerative disorders that typically develop early in life.[7] Different subtypes of PCH have been reported. PCH type 6 (PCH-6) is a specific subtype with autosomal recessive inheritance. It is an extremely rare genetic disorder. During writing this report, around 30 PCH-6 patients with RARS2 variants have been reported.[8] A homozygous or compound heterozygous mutation in the RARS2 gene is the underlying cause. RARS2 is a nuclear gene that encodes an enzyme involved in mitochondrial protein translation. The classical presentations are microcephaly, intractable seizure, and profound developmental delay.[9] [10] Most patients develop epilepsy by three months of age, which consists of focal or generalized seizures The most common of these are myoclonic, focal clonic, or generalized tonic-clonic seizures.[11] Epilepsy often becomes pharmacoresistant. Most patients present with characteristic neuroradiological abnormalities including cerebellar hypoplasia, progressive cerebral cortical atrophy, and progressive pontocerebellar atrophy.[12] Genetic testing is recommended to confirm the diagnosis.

Here, we report two siblings with PCH-6. The aim of the study is to provide insights into the clinical presentation, and diagnosis of patients with PCH-6. To the best of our knowledge, this is first reported case of PCH-6 from Bangladesh.

Case-1:

A 4-year-old girl, elder daughter of nonconsanguineous parents, had a normal perinatal period. However, at the age of two and a half months, she began experiencing eyelid myoclonia, which was treated with phenobarbitone. Later, she developed generalized tonic-clonic seizures, followed by multifocal clonic and myoclonic seizures. Additionally, she had global developmental delay.

On examination, she had microcephaly, bipyramidal sign. Her basic metabolic screening found no abnormalities. During her first EEG, multifocal epileptiform activity was observed. The 2nd EEG showed epileptic encephalopathy. MRI of the brain showed cerebral and cerebellar atrophy, hypoplasia of cerebellum and pons. The whole exome sequencing (WES) revealed compound heterozygous c.1A>G (p. Met1?) and c.574_575 delinsTT (p. Glu192leu) variant in the RARS2 gene.

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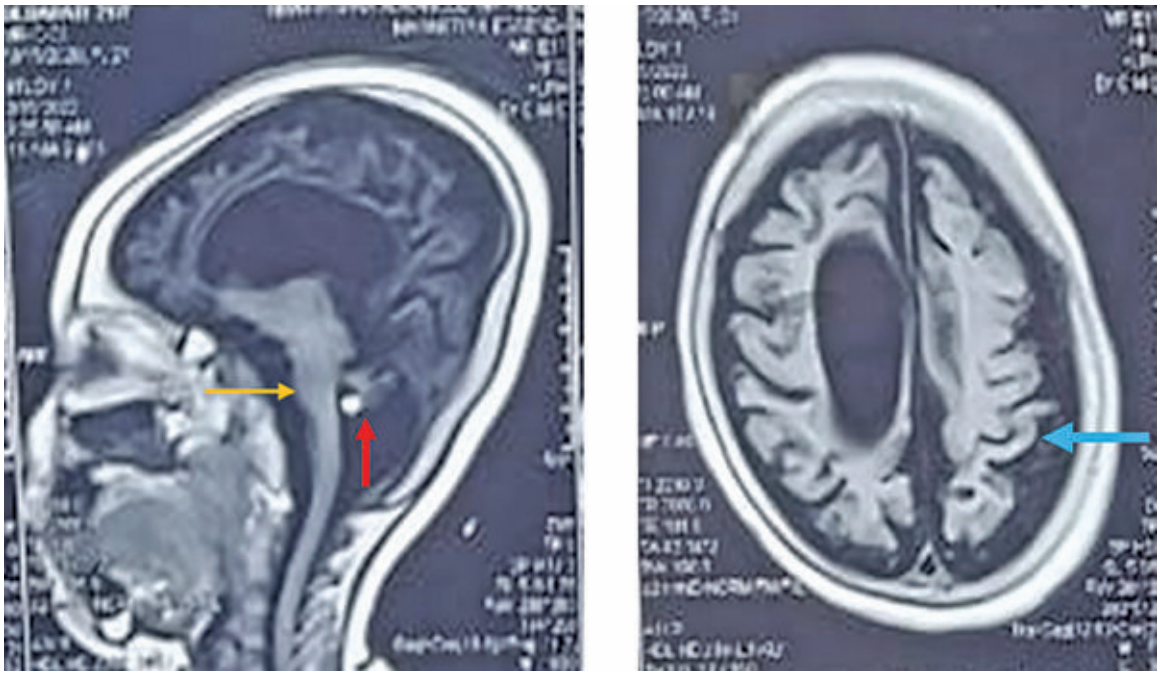

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Figure 1: *A) MRI of the brain sagittal section showed severe cerebellar atrophy (red arrow) and mild atrophy of pons (orange arrow). B) MRI of the brain axial section showed cerebral cortical atrophy (blue arrow).*

Table-I

Report of whole exome sequencing of case-1

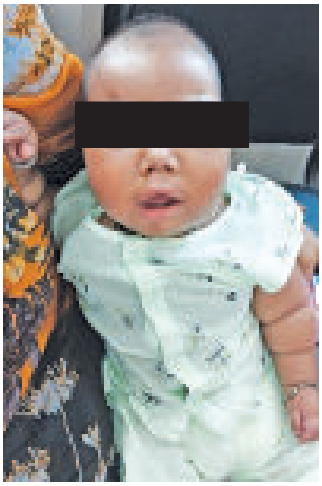
Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
***RARS2* (-)** (ENST00000369536.10)	Exon 1	c.1A>G **(p.Met1?)**	Heterozygous	Pontocerebellar hypoplasia type 6	Autosomal recessive	Pathogenic
	Exon 8	c.574_575delinsTT **(p.Glu192Leu)**	Heterozygous			Uncertain significance

Case-2:

A five-and-a-half-month-old baby, the younger sister of patient 1 was admitted to same institute due to recurrent attack of seizures and global developmental delay. Her perinatal period was also uneventful, similar to her sister.

The patient experienced the first seizure on 42nd day, which occurred multiple times in the form of repeated blinking of eyes (eyelid myoclonia) and clonic seizure of both hands. For which she was admitted to the hospital and treated with phenobarbitone and she remained seizure-free for 17 days. Later on, she developed left-sided focal clonic seizure and was treated with carbamazepine and leviracetum, resultant poor seizure control. Then she developed infantile epileptic spasm syndrome (IESS) and was treated with sodium valproate

and LEV and injectable ACTH. With this treatment, frequency of spasm started to decrease. On examination, she had dysmorphic features including open mouth, depressed nasal bridge and low set ears, microcephaly, less interested to her surroundings. She had hypertonia of limbs and no neck control. Her basic metabolic screenings were normal. The first EEG showed focal seizure and second EEG was done after developing IESS and showed modified hypsarrhythmia. MRI of the brain showed generalized cerebral atrophy and mild cerebellar atrophy. Whole exome sequencing showed compound heterozygous c.1A>G (p. Met1?) and c.574_575delinsTT (p. Glu192leu) variant in the RARS2 gene.



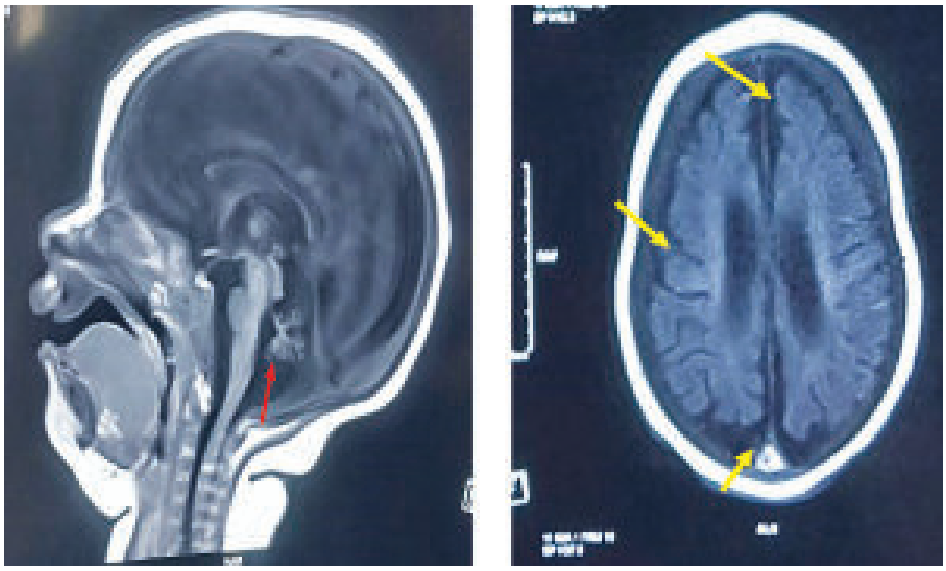


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Figure 2: *C) MRI of the brain sagittal section showed severe cerebellar atrophy (red arrow) D) MRI of the brain axial section showed cerebral cortical atrophy (yellow) arrow).*

Table-II

Report of whole exome sequencing of case-2

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
***RARS2* (-)** (ENST00000369536.10)	Exon 1	c.1A>G **(p.Met1?)**	Heterozygous	Pontocerebellar hypoplasia type 6	Autosomal recessive	Pathogenic
	Exon 8	c.574_575delinsTT **(p.Glu192Leu)**	Heterozygous			Uncertain significance

To confirm the variant, parental genetic tests were done which showed the following result:

Result: Father: heterozygous for c.574_575delinsTT variant in RARS2 gene.Mother: heterozygous for c.1A>G in RARS2 gene.

The presence of likely pathogenic variants with segregation in parents and matching phenotype confirm the diagnosis.

Discussion:

Pontocerebellar hypoplasia type 6 is an extremely rare form of PCH due to mutations in the RARS2 gene, first described in 2007.[7] Since then, around 32 patients have been reported in the literature.[13] Almost all patients presented with developmental delay, seizure, and microcephaly. It shows multiple generalized reductions in the respiratory-chain enzyme activities in muscle and elevated blood and cerebrospinal fluid lactate levels.[6] Typical MRI findings include cerebellar hypoplasia with progressive cerebellar atrophy and pons and white matter atrophy.[14] Unfortunately, treatment options are limited to symptomatic and supportive.

Most patients with PCH-6 develop severe epilepsy, experiencing their first seizure by three months of age.[5] In our cases, seizures started within three months of age in both siblings. Patient 1 had seizure at two and a half months and patient 2 at 42 days of age. Both patients experienced severe epilepsy, first developing eyelid myoclonia then focal motor seizures, and subsequently IESS. Epilepsy in PCH-6 disorder often becomes pharmacoresistant which was observed in both the cases.[3] Ngoh et al found similar findings.[15]

Dysmorphology in PCH-6 disorders has been observed in less than 20% of patients.[16] Dysmorphisms are not cardinal features and do not follow a specific pattern in this disorder. Our second patient exhibited dysmorphic features similar to those described in the case report by Nevalinaa et al.[11]

Microcephaly is also commonly observed in PCH-6 disorders.[17] Both of our patients had severe microcephaly, consistent with previously published reports.[2 6 10 11]

Patients with PCH-6 often have metabolic abnormalities, with lactic acidosis being the most common.[10] It has been observed in approximately 40% of cases.[10 18] However, our patients did not show elevated lactate in blood and CSF which was contrary with the findings of previous studies.[6 7]

In this report, patient 1 had cerebral and cerebellar atrophy, hypoplasia of the cerebellum, and pons which is typical for PCH-6. However, patient 2 had only cerebral and cerebellar atrophy. Cerebral and cerebellar atrophy without pontine atrophy has been reported by Nishri et al[13].

Which is consistent with the findings of patient 2.

Whole exome sequencing showed compound heterozygous c.1A>G (p. Met1?) and c.574_575delinsTT (p. Glu192leu) variants in two siblings of this report. The variant c.1A>G was inherited from the mother and was likely pathogenic, while c.574_575delinsTT was inherited from the father, that has not been previously described, is the variant of unknown significance. Taking into consideration the clinical presentation of the two patients, the MRI findings, and the fact that the mutation segregates with PCH in the family we think c.574_575delinsTT variant is likely pathogenic. Our report has uncovered new pathogenic variants that were previously unknown in this condition, thus broadening the range of identified variants.

Conclusion:

The findings of this report will expand our knowledge and deepen the understanding of PCH type 6. We recommend for genetic testing for patients with early onset intractable epilepsy, postnatal microcephaly, and developmental delays.

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