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| JournalName: | [**AsianJournalofMedicineandHealth**](https://journalajmah.com/index.php/AJMAH) |
| ManuscriptNumber: | **Ms\_AJMAH\_137280** |
| TitleoftheManuscript: | **Type2APontocerebellarHypoplasia,ARareCauseofPsychomotorDelay:ACaseReport** |
| TypeoftheArticle | **Casereport** |

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| **PART1:Comments** | | |
|  | **Reviewer’scomment**  **ArtificialIntelligence(AI)generatedorassistedreviewcommentsarestrictlyprohibitedduringpeerreview.** | **Author’sFeedback**(Itismandatorythatauthorsshouldwritehis/her feedback here) |
| **Pleasewriteafewsentencesregardingtheimportance of this manuscript for the scientific community. A minimum of 3-4 sentences may be required for this part.** | The relevance of this work is due to the rarity of the disease, the diagnostic challenges, and the lack of specific treatment.Thearticleisvaluableforclinicians,pediatricians,neurologists,andgeneticists,asitdrawsattentionto the early signs of PCH2A and emphasizes the importance of a multidisciplinary approach. The article describes the methods of diagnosis of this disease, which is an important clue for doctors to establish the diagnosis. | This study aims to present a clinical case of pontocerebellar hypoplasia type 2, characterized by early-onset clinical manifestations, highlighting the importance of considering this diagnosis in any case of psychomotor delay and epilepsy. |
| **Isthetitleofthearticlesuitable?**  **(Ifnotpleasesuggestanalternativetitle)** | Yes | yes |
| **Is the abstract of the article comprehensive? Do you suggesttheaddition(ordeletion)ofsomepointsinthis section? Please write your suggestions here.** | Yes,anabstractinthisformmaybeappropriate.Overall,theabstractrevealsthemainpurposeofthearticle. | yes |
| **Isthemanuscriptscientifically,correct?Pleasewrite here.** | Ibelievethatthearticleneedsto becorrected and thefollowing informationadded:1.In theIntroduction section, itisnecessary to add moreinformation aboutthediseaseitself,fromhistory tonewdata,whether itisdiagnostics or treatment(be sure toprovide referencestodifferentauthors). Write how often thisdisease occurs, what are the risk factors for this disease, describe in more detail the clinical symptoms of the disease and the value of diagnostic methods (also provide references to articles or books). 2. In the case presentation section, describe moreextensivelyandconsistently:thechild'smedicalhistory,how,whenandfromwhatdidthesymptomsbegin, what and when did the following symptoms join? What treatment was offered and in what sequence, its results? Describe the chronology of neurological symptoms. Was an MRI done in dynamics, an EEG in dynamics? At what age was a genetic test performed? Describe the MRI data in full. In the “Discussion” section, provide data on the differential diagnosis, with which diseases should a differential diagnosis be made? Comparison with the literature   * Doesthedescribedcasecorrespondtowhatisalreadyknown?   (Forexample:“Comparedtootherdescriptions,inourcaseasomewhatmilderclinicalpicturewas observed…”). Possible difficulties in diagnosis and management   * Whyisthediseasedifficulttodetect? * Whaterrorsordelayscan occur?   4.Significanceforclinicalpractice   * Whatcandoctorslearnfromthiscase?   (Forexample:“ThiscaseemphasizestheneedforearlyMRIandtheinvolvementofgeneticcounseling in developmental delay.”). In the “Conclusion” section, I think it is necessary to write Suggestions for future research   * Shouldthisdiseasebestudiedinmoredepth? * Whatquestionsremainopen? | 1. INTRODUCTION   Pontocerebellar hypoplasia type 2 (PCH2) is a rare neurodegenerative and genetic disorder with autosomal recessive inheritance, with limited treatment options (1). PCH2 was first described by Bart in 1979 and was later better characterized through genetic studies, particularly in 2009, which identified the mutation in the **TSEN54** gene (2). It is characterized by pontocerebellar hypoplasia associated with progressive neocortical atrophy. It is the most common form of pontocerebellar hypoplasia.The clinical presentation in the neonatal period is typically marked by dysphagia, respiratory distress, and feeding difficulties.The diagnosis is based on a combination of clinical and neuroradiological findings. The genetic study confirms the diagnosis by identifying a **p.A307S mutation in the TSEN54 gene**, which is present in **ninety percent of cases** (3). Our objective is to describe the clinical, radiological, and genetic features through a medical case report.   1. CASE PRESENTATION   A 4-year-old girl, born at term via non-instrumental vaginal delivery, with no history of perinatal asphyxia, from a consanguineous marriage. There is no known family history of similar cases. Since the neonatal period, she has presented with feeding difficulties and axial hypotonia. At the age of 5 months, she exhibited psychomotor delay (absence of head control, standing position, and speech), generalized epilepsy, and dyskinesia. At the age of 3 years, she experienced an episode of bacterial pneumonia.  Clinical examination revealed microcephaly, failure to thrive, spasticity, and clonus of the extremities. Brain MRI performed at 1 year of age showed hypoplasia of the cerebellar vermis. No follow-up dynamic MRI has been conducted. EEGs performed at 5 months, 1 year, 2 years, and 4 years demonstrated slowing of background activity relative to her age. Genetic analysis, conducted at the age of 2, identified a homozygous autosomal mutation in the **TSEN54** gene, located on the long arm of chromosome 17 at **17q25.1**, confirming the diagnosis of **pontocerebellar hypoplasia type 2A**. Therapeutically, the child is being treated with **Levetiracetam**, **Clobazam**, and **Trihexyphenidyl**.   1. discussion   Pontocerebellar Hypoplasia Type 2 is a rare and severe neurodegenerative disorder, primarily affecting psychomotor development.This autosomal recessive condition is characterized by the underdevelopment and degeneration of key structures in the brainstem and cerebellum, leading to profound neurological impairment, without signs of either spinal or peripheral involvement (4).  PCH2 typically presents with severe psychomotor delay, microcephaly, and early-onset extrapyramidal movement disorders such as chorea, dystonia, or dyskinesia. Neonatal symptoms often include feeding difficulties, respiratory issues, and clonus, which progress to more severe symptoms such as spasticity, epilepsy, and motor impairments. The clinical presentation can vary significantly, which has led to the identification of two distinct groups: one with dyskinesia/dystonia and severe infratentorial hypoplasia, and another with neonatal onset and polyhydramnios, hyperekplexia, and a more rigid, akinetic presentation. These differences highlight the complexity of the disease and underscore the importance of recognizing its varied manifestations (5) (6) (7) (8). Epilepsy is a frequently observed symptom, with a risk that increases with age, and can be very difficult to distinguish clinically from dyskinesias (9).  Imaging plays a crucial role in the diagnosis of PCH2, with MRI scans typically showing severe hypoplasia or flattening of the pons, cerebellar vermis, and hemispheres. The cerebellar structures often appear "wing-like," which can serve as a distinctive imaging feature. However, it is important to note that the severity of the neuroimaging findings does not always correlate with the clinical outcomes. This discrepancy emphasizes the importance of a comprehensive diagnostic approach that includes clinical, genetic, and radiological data (5) (10) (11).  Pontocerebellar hypoplasia type 2 is caused by mutations in the TSEN54 gene, located on chromosome 17, which is involved in the maturation of transfer RNAs (tRNAs). Mutations in this gene disrupt normal cellular processes, leading to cerebellar and pontine hypoplasia. The autosomal recessive inheritance pattern of PCH2 is commonly seen in consanguineous families, which further underscores the importance of genetic counseling and early diagnosis in affected populations (12).  In addition to the primary neurological manifestations, patients with PCH2 may experience other complications, such as episodes of rhabdomyolysis and, rarely, Reye-like syndrome (13). These complications highlight the need for comprehensive management strategies that address not only the central nervous system involvement but also other organ systems potentially affected by the disorder.  The differential diagnosis of pontocerebellar hypoplasia type 2A (PCH2A) includes other forms of PCH, particularly type 1, which is distinguished by associated spinal cord involvement, as well as types 4 and 6, which share some clinical and radiological features but differ in genetic origin and disease progression (14)(15). The CASK-related syndrome should also be considered, as its clinical presentation may mimic that of PCH2A, with a combination of microcephaly, hypotonia, epilepsy, and neurodevelopmental delay. However, it is differentiated by the potential presence of ophthalmological abnormalities (16)(17). Certain congenital malformations of the cerebellum or brainstem may resemble PCH2, but they are usually associated with other radiological findings, such as cysts or anomalies of the corpus callosum (16).  Treatment is symptomatic and focuses on managing dystonia, dyskinesia, and seizures, as well as feeding the patient through a percutaneous endoscopic gastrostomy tube.  This case highlights the importance of clinical examination during the neonatal period, as well as the need for early MRI and genetic counseling in cases of developmental delay.   1. Conclusion   Pontocerebellar hypoplasia type 2A is often fatal in early childhood. Potentially life-threatening complications include sleep apnea, rhabdomyolysis, and malignant hyperthermia. In the parents of an affected child, the risk of having another affected child is 25%, highlighting the importance of genetic counseling with targeted genetic testing in the parents. Despite recent advances, several questions remain unanswered, warranting further research, particularly regarding therapeutic possibilities. |
| **Arethereferencessufficientandrecent?Ifyouhave suggestions of additional references, please mention them in the review form.** | Ithinkthatmorearticlesshouldbeaddedtotheliterature,preferablynewerones.Forexample: “What’snewin pontocerebellar hypoplasia? An update on genes and subtypes Tessa van Dijk, Frank Baas, Peter G. Barth &Bwee Tien Poll-The Orphanet Journal of Rare Diseases volume 13, Article number: 92 (2018)”. | References   1. Kagermeier, T., Hauser, S., Sarieva, K., Laugwitz, L., Groeschel, S., Janzarik, W.G., Yentür, Z., Becker, K., Schöls, L., Krägeloh-Mann, I., & Mayer, S. (2024). Human organoid model of pontocerebellar hypoplasia 2a recapitulates brain region-specific size differences. Disease Models & Mechanisms, 17(7), dmm050740. 2. The University of Chicago Genetic Services Laboratories. (2013). Next Generation Sequencing Panel for Cerebellar Hypoplasia. Chicago, IL: The University of Chicago. 3. Sánchez-Albisua, I., Frölich, S., Barth, P. G., Steinlin, M., & Krägeloh-Mann, I. (2014). Natural course of pontocerebellar hypoplasia type 2A. Orphanet Journal of Rare Diseases, 9, 70 4. Sans-Fitó, A., Campistol-Plana, J., Mas-Salguero, M. J., Póo-Argüelles, P., & Fernández-Alvarez, E. (2002). Pontocerebellar hypoplasia type 2 and Reye-like syndrome. Journal of Child Neurology, 17(2), 132–134 5. Barth, P., Blennow, G., Lenard, H., Begeer, J., Van Der Kley, J., Hanefeld, F., Peters, A., &Valk, J. (1995). The syndrome of autosornal recessive pontocerebellar hypoplasia, microcephaly, and extrapyramidal dyskinesia (pontocerebellar hypoplasia type 2). *Neurology*, 45, 311 - 317. 6. Steinlin, M., Klein, A., Haas-Lude, K., Zafeiriou, D., Strozzi, S., Müller, T., Gubser-Mercati, D., Mechelke, T., Krägeloh-Mann, I., &Boltshauser, E. (2007). Pontocerebellar hypoplasia type 2: variability in clinical and imaging findings.. *European journal of paediatricneurology : EJPN : official journal of the European Paediatric Neurology Society*, 11 3, 146-52 . 7. Coppola, G., Muras, I., &Pascotto, A. (2000). Pontocerebellar hypoplasia type 2 (PCH2): report of two siblings. *Brain and Development*, 22, 188-192. 8. Cohen, R., Goldberg-Stern, H., Kivity, S., Halevy, A., Aharoni, S., Kornreich, L., & Straussberg, R. (2020). Evolution of EEG Findings in Pontocerebellar Hypoplasia Type 2A: Normal EEG in the First Few Months followed by Abnormal Tracing over the Years. Neuropediatrics, 51(6), 440–444. 9. Barth, P., Aronica, E., De Vries, L., Nikkels, P., Scheper, W., Hoozemans, J., Poll‐The, B., &Troost, D. (2007). Pontocerebellar hypoplasia type 2: a neuropathological update. *ActaNeuropathologica*, 114, 373 - 386. 10. Grellner, W., Rohde, K., &Wilske, J. (2000). Fatal outcome in a case of pontocerebellar hypoplasia type 2.. *Forensic science international*, 113 1-3, 165-72 . 11. Battini, R., D'Arrigo, S., Cassandrini, D., Guzzetta, A., Fiorillo, C., Pantaleoni, C., Romano, A., Alfei, E., Cioni, G., &Santorelli, F. (2014). Novel Mutations in TSEN54 in Pontocerebellar Hypoplasia Type 2. *Journal of Child Neurology*, 29, 520 - 525.. 12. Zafeiriou, D., Ververi, A., Tsitlakidou, A., Anastasiou, A., &Vargìami, E. (2013). Recurrent episodes of rhabdomyolysis in pontocerebellar hypoplasia type 2. *Neuromuscular Disorders*, 23, 116-119. 13. Barth, P. (1993). Pontocerebellar hypoplasias An overview of a group of inherited neurodegenerative disorders with fetal onset. *Brain and Development*, 15, 411-422. 14. Namavar, Y., Barth, P., Kasher, P., Van Ruissen, F., Brockmann, K., Bernert, G., Writzl, K., Ventura, K., Cheng, E., Ferriero, D., Basel‐Vanagaite, L., Eggens, V., Krägeloh-Mann, I., De Meirleir, L., King, M., Graham, J., Von Moers, A., Knoers, N., Sztriha, L., Korinthenberg, R., Dobyns, W., Baas, F., & Poll‐The, B. (2011). Clinical, neuroradiological and genetic findings in pontocerebellar hypoplasia.. *Brain : a journal of neurology*, 134 Pt 1, 143-56 . 15. Rüsch, C., Bölsterli, B., Kottke, R., Steinfeld, R., & Boltshauser, E. (2020). Pontocerebellar Hypoplasia: a Pattern Recognition Approach. *The Cerebellum*, 19, 569 - 582. 16. Burglen, L., Chantot-Bastaraud, S., Garel, C., Milh, M., Touraine, R., Zanni, G., Petit, F., Afenjar, A., Goizet, C., Barresi, S., Coussement, A., Ioos, C., Lazaro, L., Joriot, S., Desguerre, I., Lacombe, D., Portes, D., Bertini, E., Siffroi, J., De Villemeur, B., & Rodriguez, D. (2012). Spectrum of pontocerebellar hypoplasia in 13 girls and boys with CASK mutations: confirmation of a recognizable phenotype and first description of a male mosaic patient. *Orphanet Journal of Rare Diseases*, 7, 18 - 18. |

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| **Isthelanguage/Englishqualityofthearticlesuitable for scholarly communications?** | Yes | yes |
| **Optional/General**comments | Thearticlecanbepublishedafteralltheseadditions. | yes |

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| **PART 2:** | | |
|  | **Reviewer’s comment** | **Author’s comment***(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
| **Are there ethical issues in this manuscript?** | *(If yes, Kindly please write down the ethical issues here in details)* |  |