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Original Article

Diagnostic Clues and Pitfalls in Pontocerebellar Hypoplasia Type 2A

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ABSTRACT

Background: Pontocerebellar hypoplasia type 2A (PCH2A) is a rare autosomal recessive neurodegenerative disease caused by a specific pathogenic variant in the TSEN54 gene (p.A307S). Affected children show early but initially unspecific symptoms, diagnosed primarily through postnatal magnetic resonance imaging (MRI), with confirmation by genetic testing. This study examines the diagnostic process and key considerations for accurate diagnosis.
Methods: We retrospectively collected data from 65 children (33 girls, 32 boys) with genetically confirmed PCH2A as part of a Natural History Study. Data were gathered via parental questionnaires, interviews, and medical reports. The cohort was divided into two groups based on year of birth: children born before (n = 30) and after (n = 35) the identification of the pathogenic variant in 2008.
Results: Prenatally, in 4 of 21 cases with specialized ultrasound (gestational weeks 12-32), only unspecific cerebellar abnormalities were reported. One fetal MRI (week 31) revealed clear cerebellar hypoplasia, in two others (week 21 and 31), slight cerebellar abnormalities were reported. Postnatal neurosonography often indicated disease features (26/54), later confirmed by MRI (62/63). Clinical symptoms appeared at a median age of 0 months (range 0-6 months), often initially suggesting acute rather than congenital issues. In the group born after 2008, median time from first symptoms to genetic confirmation was 5 months.
Conclusions: PCH2A presents early with nonspecific symptoms. Prenatal and postnatal ultrasound imaging can fail to detect the condition, with MRI being the gold standard for diagnosis. Over time, the diagnostic process, including genetic confirmation, has become faster.

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Introduction

Pontocerebellar hypoplasia (PCH) refers to a heterogeneous and expanding group of rare, predominantly neurodegenerative disorders inherited in an autosomal recessive manner. These conditions primarily affect the cerebellum and pons, though they may also involve supratentorial brain structures.[1,2] The most common subtype is pontocerebellar hypoplasia type 2A (PCH2A) with an estimated incidence of 1:200.000 live births.[3] It is a well-defined and homogeneous disorder caused by a homozygous pathogenic variant in the *TSEN54* gene (p.A307S), which probably alters tRNA processing and mRNA modification.[3-6]

Prenatal imaging in PCH2A if often reported as normal, although subtle abnormalities may occasionally be detected. Some reports describe a reduced transcerebellar diameter (TCD) on prenatal imaging, as well as mild clinical findings, such as head circumference at the lower limit of normal, polyhydramnios, or abnormal fetal movements.[3,7-9]

Postnatally, affected children typically present with symptoms within the first days of life.[3,7] Newborns with PCH2A often show feeding difficulties, excessive crying, altered muscle tone, and episodes of drowsiness or restlessness.[2,3,5] A hallmark feature is progressive microcephaly, although head circumference at birth is often within the lower normal range.[10,11]

In infancy and early childhood, more specific symptoms emerge, including a dyskinetic movement disorder, global developmental delay, severe gastroesophageal reflux, episodic pain episodes with restlessness, and, later on, epileptic seizures.[1,3,5,12] The overall life expectancy of children with PCH2A is significantly reduced. Earlier estimations suggested a 10-year survival of around 50%, while more recent data, including our cohort, indicate a 10-year survival of approximately 70%.[3,11]

For families with a known history of PCH2A, prenatal genetic testing can provide a reliable diagnosis.[13] However, due to the autosomal recessive inheritance pattern, many parents are unaware of the genetic risk until a child is diagnosed with PCH2A. Postnatally, the diagnosis is typically suggested by magnetic resonance imaging (MRI) findings and confirmed through genetic testing.[3,7]

On postnatal MRI, the characteristic PCH often appears in a so-called *"dragonfly"* configuration, with relative sparing of the cerebellar vermis.[14,15] Additional supratentorial abnormalities, such as cerebral atrophy, ventriculomegaly, and delayed myelination, have also been reported.[7,10,14,16,17]

Differential diagnoses—clinically and radiologically—include other forms of PCH, Hoyeraal–Hreidarsson syndrome, congenital disorders of glycosylation, or infratentorial malformations such as Dandy–Walker syndrome, all of which can present with reduced cerebellar volume or be misinterpreted as such.[1,2,14,18] Notably, brain lesions in extremely preterm infants can also mimic PCH.[2,19]

This retrospective study of 65 patients with genetically confirmed PCH2A aims to assess the diagnostic value and limitations of prenatal and postnatal imaging and early clinical signs, with a focus on potential diagnostic pitfalls and misinterpretations on the way to the final diagnosis.

Materials and Methods

Clinical data of patients with genetically confirmed PCH2A were retrospectively collected via digital questionnaires completed by parents. The study was approved by the Ethics Committee of the University of Freiburg (approval no. 20-1040). Previous data originated from a Natural History Study (NHS) approved by the Ethics Committees of the University of Tübingen in 2012 (approval no. 105/2012BO2) and 2021 (approval no. 961/2020BO2). Written informed consent was obtained from all parents.

The study focused on pregnancy-related factors and diagnostic procedures. Not all parents answered every question, and some questions allowed multiple responses; therefore, reported percentages do not always refer to the full cohort (N = 65).

Medical records and neuroimaging data were reviewed to supplement parent-reported information. In most cases, original radiology reports were available and compared with parental reports. Discrepancies or missing information were clarified through follow-up telephone interviews. For preterm infants, corrected age was used when analyzing MRI timing and other clinical data.

Neuroimaging data were collected across four countries and over a wide time span, ranging from the early 1990s to examinations performed shortly before questionnaire completion. Consequently, imaging data were heterogeneous with respect to acquisition protocols, MRI magnetic field strength, available sequences, and image resolution. Reported results relied on medical records, as they had been instrumental for the further diagnostic pathways. Reports were available for 50 children. Original MRI datasets were available for 53 children. Fifty were included in a morphometric analysis we had reported earlier.[16]

The aim of this study was to describe real-world diagnostic pathways leading to the diagnosis of PCH2A. In the majority of patients, no increased a priori risk for PCH2A was known at the time of pregnancy or early postnatal life. Only a minority of children had a positive family history, either involving an older sibling with confirmed or suspected PCH (n = 7) or a member of the extended family (n = 1). Additionally, in two sibling pairs, the suspected diagnosis in the older child was established only after the birth of the younger child.

To assess the impact of advances in genetic diagnostics, the time to first suspected diagnosis of PCH and the time to definitive diagnosis were compared between children born before and after 2008, the year in which the genetic basis of PCH2A was identified.[4] From 2008 onwards, genetic testing became available as a confirmatory diagnostic tool for PCH2A.[4]

Statistical analyses were performed using SPSS and Microsoft Excel. Descriptive statistics included calculation of medians and means. Group differences were assessed using the Mann–Whitney *U* test. Most results were analyzed descriptively and visualized using Microsoft PowerPoint.

Results

Study population

A total of 65 children with PCH2A were included in the study. This cohort is identical to the cohort described in our current publication by Kuhn et al.[11] Half of them (33 children) had previously participated in the initial NHS conducted 10 years earlier.[3] For 12 of these children, no follow-up data were available (one was still alive, four had passed away at the time of the first NHS, and seven were lost to follow-up). The participating families were from Germany, Switzerland, Austria, and Bulgaria. The gender distribution was even, with 33 girls (51%) and 32 boys (49%). The median age of the participants at the time of inclusion was 8.4 years, with a range of 7 months to 33 years. Of the 65 children, 42 (65%) were alive at the time of the survey, 16 (25%) had passed away, and survival status was unknown for 7 children (10%). Thirty children (46%) were born before 2008, while 35 children (54%) were born after. Nine sibling pairs were included in the study: seven pairs born before 2008, one pair born after 2008, and one pair with one child from each group.

Cerebral imaging

Prenatal cerebral imaging

Of the 65 participating children, 23 (35.4%) underwent specialized prenatal diagnostics using ultrasound (n = 21) or MRI (n = 3) (Fig 1). The median gestational age at the time of these examinations was 21 weeks (range: 12 to 32 weeks). Fetal MRI was performed in two pregnancies because of a positive family history: in one case before molecular genetic testing was available, and in another despite the availability of molecular genetic diagnostics. In the third case, fetal MRI was indicated due to nonspecific prenatal ultrasound findings, namely polyhydramnios and a reduced TCD.

Mild cerebellar abnormalities were reported in 7 of these 23 cases (30.4%): all three fetal MRIs and four ultrasound examinations. Reported findings included "cerebellar hypoplasia," "enlarged cisterna magna," "suspected Dandy–Walker syndrome," and "fluid around the cerebellum."

In two cases, fetal MRI was described as showing nonspecific posterior fossa findings in the available reports, including an "enlarged posterior fossa without cerebellar hypoplasia" at 21 weeks' gestation and "slender cerebellar hemispheres" at 31 weeks. In both cases, ultrasound at 20-21 weeks demonstrated normal TCDs. In the third case, ultrasound at 30 weeks revealed a TCD below the 5th percentile, which was confirmed by fetal MRI at 31 and 34 weeks, with no interval increase in TCD.

In addition to cerebral imaging, other specialized prenatal investigations were performed in a small number of pregnancies, including amniotic fluid analysis (3/65), as well as fetal echocardiography, Doppler studies, and nuchal translucency measurements (each 2/65). In more than half of the pregnancies (55.4%), no specialized prenatal investigations were performed.

Postnatal ultrasound

Postnatal cranial ultrasound was performed in 54 out of 65 children (83.1%), with follow-up examinations in 20 children (37%)

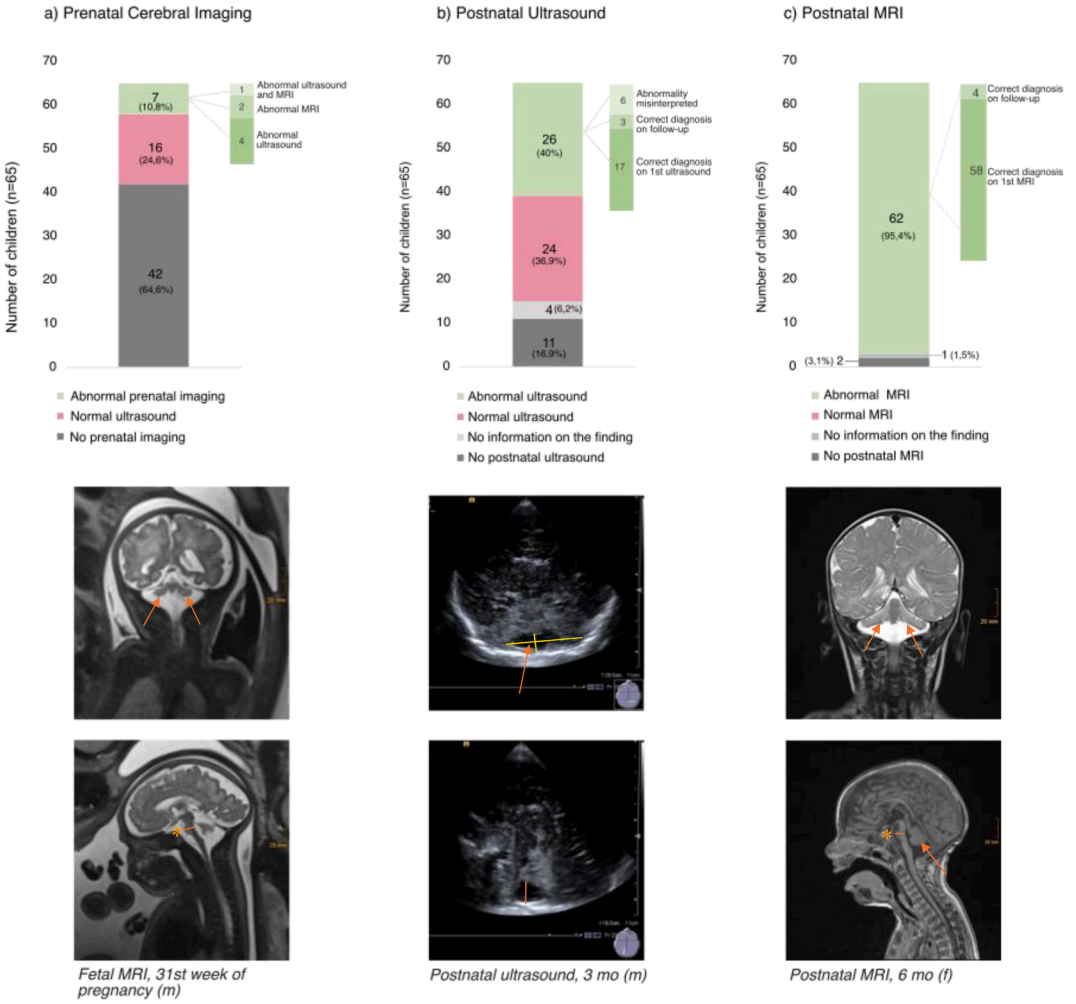

FIGURE 1. Cerebral imaging prenatal (A) and postnatal (B + C). Top: Overview of all 65 participating children and their imaging. In gray: children who did not receive the corresponding imaging. Light gray: Children for whom no information on the findings was available. Red: Children for whom the respective imaging was classified as normal. Green: Children with a pathology in the imaging. These are further subdivided for (A) prenatal imaging: from dark to light: abnormal ultrasound, abnormal MRI, both entities abnormal. Example image: Fetal T2-weighted MRI of a male fetus at 31 weeks of gestation. Coronal (top) and sagittal (bottom) views demonstrate early pontocerebellar hypoplasia with the characteristic "dragonfly" configuration of the cerebellum (arrows), while the pons appears relatively preserved at this stage (star). (B) Postnatal ultrasound: from dark to light: correct diagnosis on first ultrasound, in follow-up, findings interpreted differently (megacisterna magna, cyst). Example image: Postnatal cranial ultrasound at 3 months of age in a child with PCH2A. Coronal (top) and sagittal (bottom) images show a prominent fluid-filled space in the posterior fossa that was initially measured as a mega cisterna magna; this appearance reflects cerebellar hypoplasia rather than a primary enlargement of the cisterna magna (arrow). (C) Postnatal MRI: dark for correct diagnosis at first MRI and light for correct diagnosis during follow-up. Example image: Postnatal MRI at 6 months of age in a child with PCH2A. Coronal T2-weighted (top) and sagittal T1-weighted (bottom) images illustrate the typical "dragonfly" appearance of the cerebellum (arrows) and a flattened pons (star), consistent with pontocerebellar hypoplasia. PCH2A = pontocerebellar hypoplasia type 2A; MRI = magnetic resonance imaging.

(Fig 1). The median age at the first ultrasound was 0 months, and the latest was at 12 months. Posterior fossa abnormalities were identified in nearly half of the children (26/54), with "cerebellar hypoplasia" or "enlarged cisterna magna" observed in 20 cases, primarily during the first examination. Six additional children had posterior cranial fossa abnormalities, initially misinterpreted as "cyst" (n = 6) or "suspected Dandy–Walker syndrome" (n = 3). Twelve children (22%) had normal ultrasound findings, and data were unavailable for four children. Other findings included difficult ultrasound conditions due to narrow or prematurely closed fontanelles (n = 13), enlarged ventricles (n = 11), and abnormal gyration patterns. Detailed findings are listed in Table 1.

Postnatal MRI

All but two children underwent at least one MRI, 16 had follow-up MRIs, and seven underwent three or more scans (Fig 1). The median age at first MRI was 2.5 months. PCH or abnormal cerebellar structure was found in the majority of children. Combined anomalies of the pons and cerebellum were found in 46 of 63 children (73%), whereas 15 children had isolated cerebellar anomalies. Overall, 61 of 63 children (96.8%) showed clear imaging findings consistent with (ponto-)cerebellar hypoplasia, most of which were already apparent on the initial scan (92.1%, 58 of 63 children). In two cases, the first MRI was reported as normal, with the diagnosis established on follow-up imaging. Additionally, non–PCH-related abnormalities were frequently observed, including "ventricular enlargement" (15/63), "corpus callosum hypoplasia" (10/63), "delayed myelination" (7/63), and "thin white matter" (4/63). Dandy–Walker syndrome and Blake's pouch cyst were noted in six children, representing important differential diagnoses. Table 1 provides detailed information on the MRI findings.

Clinical findings

Pregnancy

Approximately half of the pregnancies were reported as normal (30/65; 46.2%). The most common abnormality was unusual fetal movements, such as twitching or trembling (18/65; 27.7%), with either increased (8/65) or decreased (6/65) movement patterns. Polyhydramnios occurred in 12 of 65 pregnancies (18.5%) and oligohydramnios in one. Other findings included microcephaly (4 children) and intrauterine growth retardation (3 children). All pregnancy-related symptoms are visualized in Fig 2.

Birth

Most children were born full-term, with a median gestational age of 39 weeks and 4 days. Three children were born preterm, at 30 + 4, 36 + 0, and 36 + 4 weeks. Apgar scores at 5 and 10 minutes were mostly between 9 and 10. Umbilical artery pH values were normal in most children, though nine (17.3%) had acidotic values (≤7.2). Birth complications included shoulder dystocia (n = 4), meconium-stained amniotic fluid (n = 3), and breech presentation (n = 2), as reported by parents. In four cases, parents stated that their children were born by caesarean section.

Neonatal period

Hospital admission during the neonatal period was required for 39 of 53 children (73.6%), most commonly within the first 72 hours of life. This section refers specifically to children who were already clinically conspicuous during the neonatal period and therefore required early medical attention. Reported interventions included nasogastric tube feeding in 22 of 52 children (42%), home monitoring in 15 of 52 (28.8%), and oxygen therapy in 14 of 52 (26.9%). The most frequent neonatal problems were feeding difficulties (94%), restlessness (68%), and increased muscle tone (66%). Suspected seizures were observed in five children during the neonatal period. Further details of neonatal findings are summarized in Fig 3.

First clinical abnormalities observed by parents and pediatricians

Independently of whether children were clinically symptomatic during the neonatal period, parents were asked to report the earliest abnormalities they perceived as deviating from typical development. The earliest clinical abnormalities were predominantly reported within the first month of life (range 0-6 months). Feeding difficulties were the most frequently reported early symptom, occurring in 52 of 58 children (89.7%), followed by vomiting in 22 of 53 (41.5%), gastroesophageal reflux in 17 of 53 (32.1%), and developmental delay in 28 of 58 children (48.3%) (Fig 4).

Additional early observations included unusual movements (36/57; 62.1%), muscle hypertonia (35/55; 63.6%), hypotonia (9/52; 17.3%), myoclonus-like muscle jerks (reported as muscle trembling in the original questionnaire) in 31 of 53 children (58.5%), hyperexcitability (26/54; 48.1%), and excessive crying (16/53; 30.2%). Microcephaly was reported in 19 of 52 children (36.5%). Suspected seizures were reported by parents as one of the earliest clinical manifestations in 15 of 53 children (28.3%) and were based on parental observation without further characterization at this stage (Fig 4).

TABLE 1.
Findings in Postnatal Cerebral Ultrasound and MRI

	Postnatal Ultrasound	Postnatal MRI
Differential diagnosis/ misinterpretation	• Megacisterna magna: 11/54 (20.4%) • Dandy–Walker: 3/54 (5.6%) • Cyst: 6/54 (11.1%)	• Megacisterna magna: 12/63 (19%) • Dandy–Walker: 5/63 (7.9%) • Blake-Pouch: 1/63 (1.6%)
Additional findings	• Ventricular system*: 11/54 (20.4%) • Narrow corpus callosum: 2/54 (3.7%) • Narrow fontanelle: 13/54 (24.1%) • Intraventricular hemorrhage: 3/54 • Other: Cyst in lateral ventricle/plexus (2/54), gyration anomaly (1/54)	• Ventricular system†: 15/63 (23.8%) • Narrow corpus callosum: 10/63 (15.9%) • Supratentorial: Volume reduction (7/63), delayed myelination (7/63), white matter anomalies (4/63), incomplete opercularization (3/63), gyration anomaly (2/63), SDH/SAB (1/63) • Other (each 1/63): Hemorrhage in posterior cranial fossa, edematous pons, arachnoid cyst, hemodynamic infarcts

Abbreviation:
MRI = Magnetic resonance imaging

* Ventricular abnormalities on ultrasound included global or borderline ventricular enlargement (n = 4), mild lateral ventricular dilatation (n = 2), isolated fourth ventricle enlargement (n = 3), abnormal frontal horn configuration (n = 1), combined ventricular and extra-axial CSF space enlargement (n = 1), and a focal cystic ventricular abnormality (n = 1).

† Ventricular abnormalities on MRI included combined enlargement of inner and outer CSF spaces (n = 7), predominant outer CSF space enlargement (n = 1), predominant ventricular enlargement (n = 2), nonspecified CSF space enlargement (n = 3), mild CSF flow disturbance (n = 2).

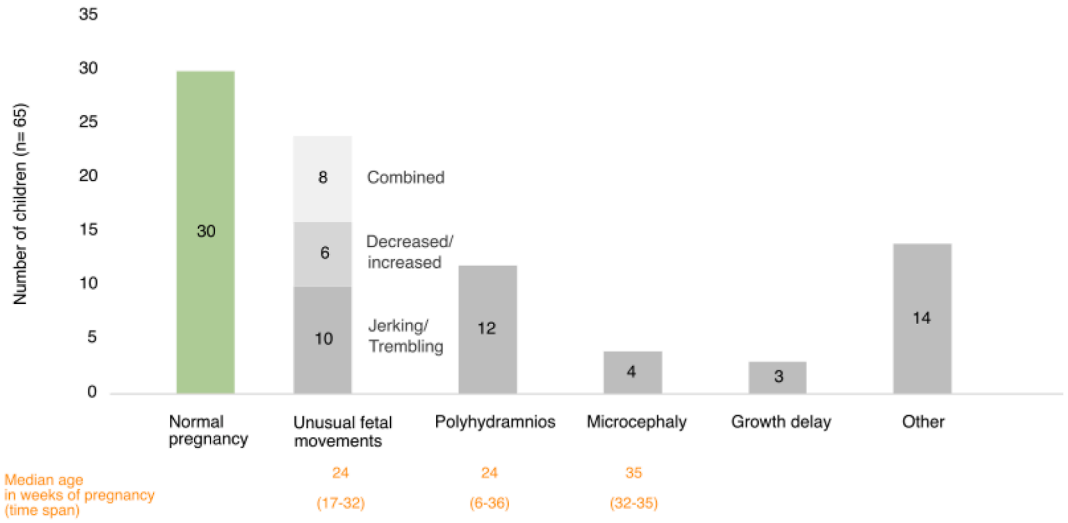

FIGURE 2. Abnormalities in pregnancy and the median age of their occurrence. Answers to the question of which symptoms the mothers observed during pregnancy. Multiple answers were possible. The left-hand bar (green) shows all children whose pregnancy was completely normal.

Overall, the majority of children developed noticeable clinical abnormalities early in infancy, most commonly within the first 2 months of life, with a median age at first reported abnormalities of one month (Fig 5).

Based on the review of medical reports and parental recollection of information communicated by treating pediatricians, feeding difficulties and abnormal cerebral ultrasound findings were most frequently documented as the earliest abnormalities

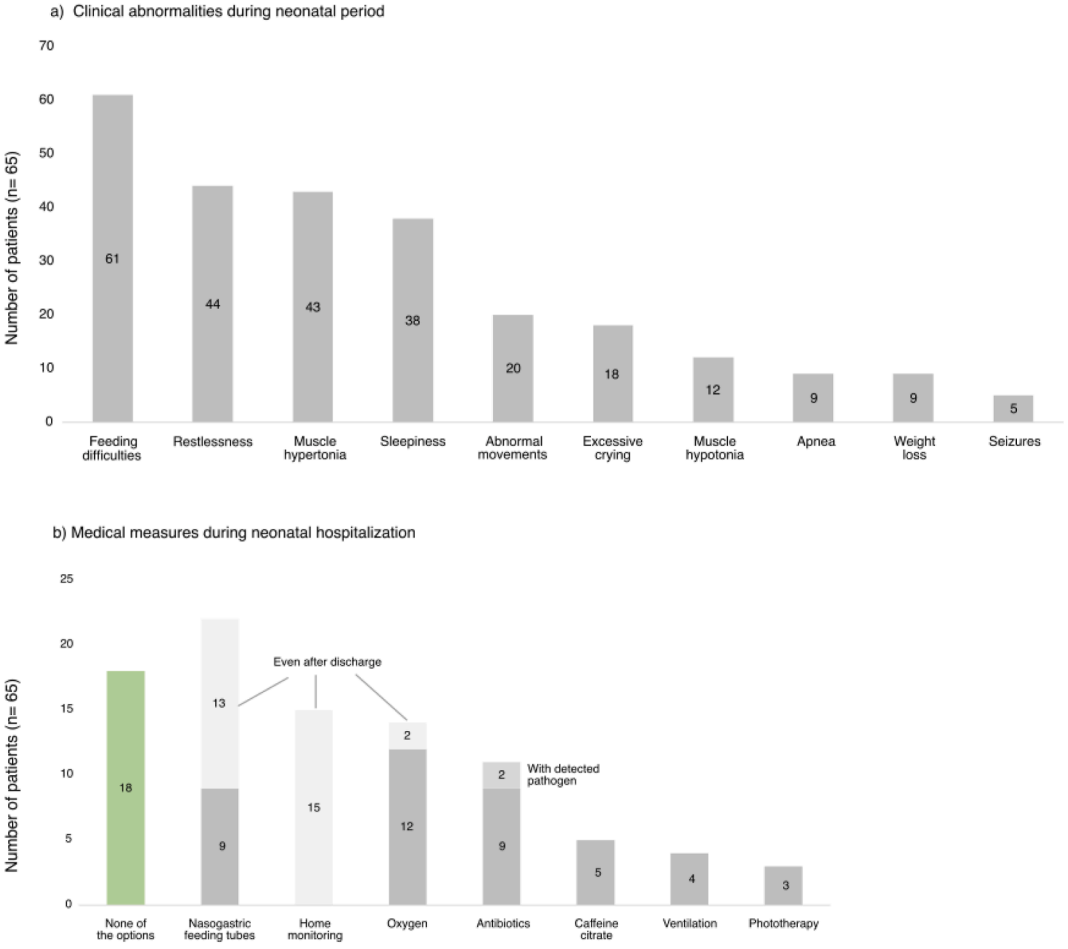

FIGURE 3. Symptoms and therapeutic measures during the neonatal period. (A) Symptoms during the neonatal period, observed by parents and treating physicians, multiple answers possible. (B) Therapeutic measures that were necessary for children who had to remain hospitalized after birth (n = 39), multiple answers possible.

noted by health care professionals. Further details are provided in Fig 4.

Timeframe of diagnostic milestones

Children born before and after 2008 were compared regarding diagnostic milestones (see also Table 2). Parents were informed that PCH was suspected at a median age of 4 months. The difference between the two groups was not significant ($P = 0.13$), with a median age of suspected diagnosis of 5 months (range: 0-364 months) for children born before 2008, and 4 months (range: 0-48 months) for those born after 2008. Genetic testing confirmed the diagnosis in 59 children (91%), with children born after 2008 being diagnosed at a median age of 8 months, compared to 4.75 years for those born before 2008. The time from first symptoms to genetic confirmation was significantly shorter for children born after 2008 (median 5 months) than for those born earlier (median 4.6 years). All median ages and quantiles are visualized in Fig 5. The results of the Mann-Whitney *U* test revealed a significant difference between the two groups only for genetic testing ($U = 70.5$, $Z = -5.399$, $P < 0.001$), with higher ranks observed in the pre-2008 group. This was also reflected in the time span from the first symptoms to the genetic test ($U = 61.5$, $Z = -5.538$, $P < 0.001$). The mean age at all other diagnostic steps did not significantly differ.

Discussion

Prenatal diagnosis of PCH2A

Prenatal diagnostic findings in PCH2A are rarely reported, and pregnancies are frequently described as uneventful.[2,7,9,13] In our cohort, prenatal ultrasound abnormalities in fetuses with PCH2A were generally vague and poorly quantified, particularly with respect to cerebellar hypoplasia. Retrospective review suggests that some of these nonspecific findings may, in fact, represent early disease-related alterations. In at least one case, the TCD measured in the third trimester was below the 5th percentile, with no interval growth between 31 and 34 weeks of gestation, pointing toward impaired cerebellar development and/or early neurodegeneration.

The TCD is a key biometric marker for assessing cerebellar development and can be measured by both prenatal ultrasound and fetal MRI.[8,20-22] Reduced TCD has been described at birth in several PCH subtypes, including PCH2A.[8,16,23] In a heterogeneous cohort of fetuses with PCH, including three with PCH2A, Jaillard et al. demonstrated that deviations from normal TCD values become more pronounced toward the end of gestation, coinciding with the phase of accelerated cerebellar growth in the third trimester.[8] As only three of 42 fetuses with reduced cerebellar biometry in that study were ultimately diagnosed with PCH2A—the most common postnatal PCH subtype—the authors concluded that TSEN54-related PCH is rarely detected prenatally.[8]

Although imaging abnormalities consistent with PCH2A may be detectable during pregnancy, they often remain unrecognized in routine clinical assessment of a presumed uncomplicated pregnancy. Several factors likely contribute to this. From a clinical perspective, awareness of this rare disease entity remains limited. From a technical standpoint, prenatal ultrasound has restricted spatial resolution of posterior fossa structures. Moreover, physiological cerebellar growth accelerates predominantly in the third trimester, rendering early deviations from normal development subtle at the time of routine second-trimester anomaly screening.[24,25]

Prenatal diagnosis of PCH2A is particularly challenging in the absence of a positive family history. In our cohort, none of the children born after 2008—when molecular genetic confirmation of PCH2A became available—underwent prenatal genetic testing, underscoring persistent under-recognition of the condition.[4] Even in pregnancies with a known family history of PCH2A, prenatal imaging did not lead to a prenatal diagnosis, and genetic testing was either not yet available or not initiated due to low clinical suspicion.

Fetal MRI has been shown to allow accurate prenatal diagnosis of PCH, with certain imaging features predicting classic PCH phenotypes.[8] While fetal MRI provides superior visualization of posterior fossa structures compared to ultrasound, it may still fail to identify PCH2A earlier in pregnancy in routine clinical practice for the reasons outlined above. Advanced techniques—such as fetal diffusion-weighted tractography, which could demonstrate the reduction of transverse pontocerebellar fibers, a pathognomonic feature of PCH2A—are not routinely available.[13] Quantitative volumetric analysis of prenatal MRI data may further improve early detection in the future.[10,16]

Due to the retrospective design of our study, data on medically indicated pregnancy terminations were not available. Nevertheless, the high number of affected siblings born before 2008 suggests that improved access to and awareness of prenatal and preimplantation genetic testing could substantially enhance early diagnosis and informed reproductive decision-making in families at risk.

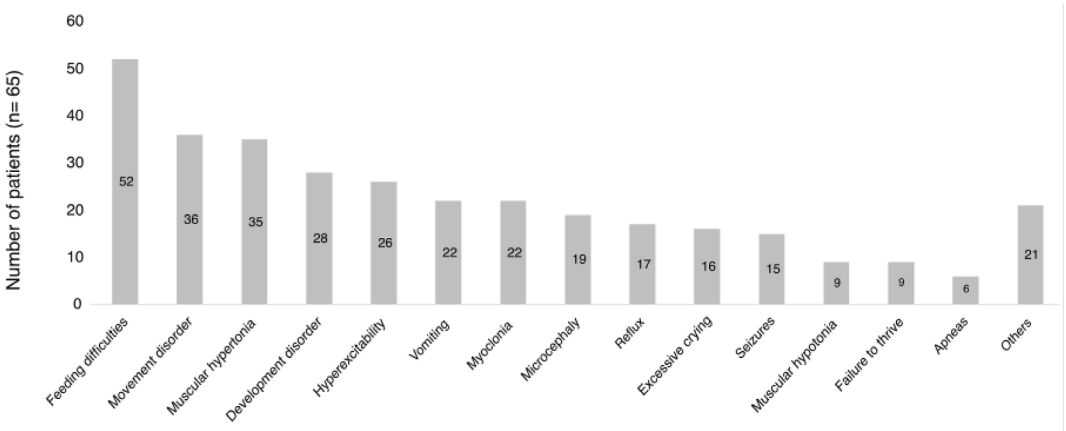

FIGURE 4. First clinical findings of PCH2A as observed by parents. Multiple answers possible. PCH2A = pontocerebellar hypoplasia type 2A.

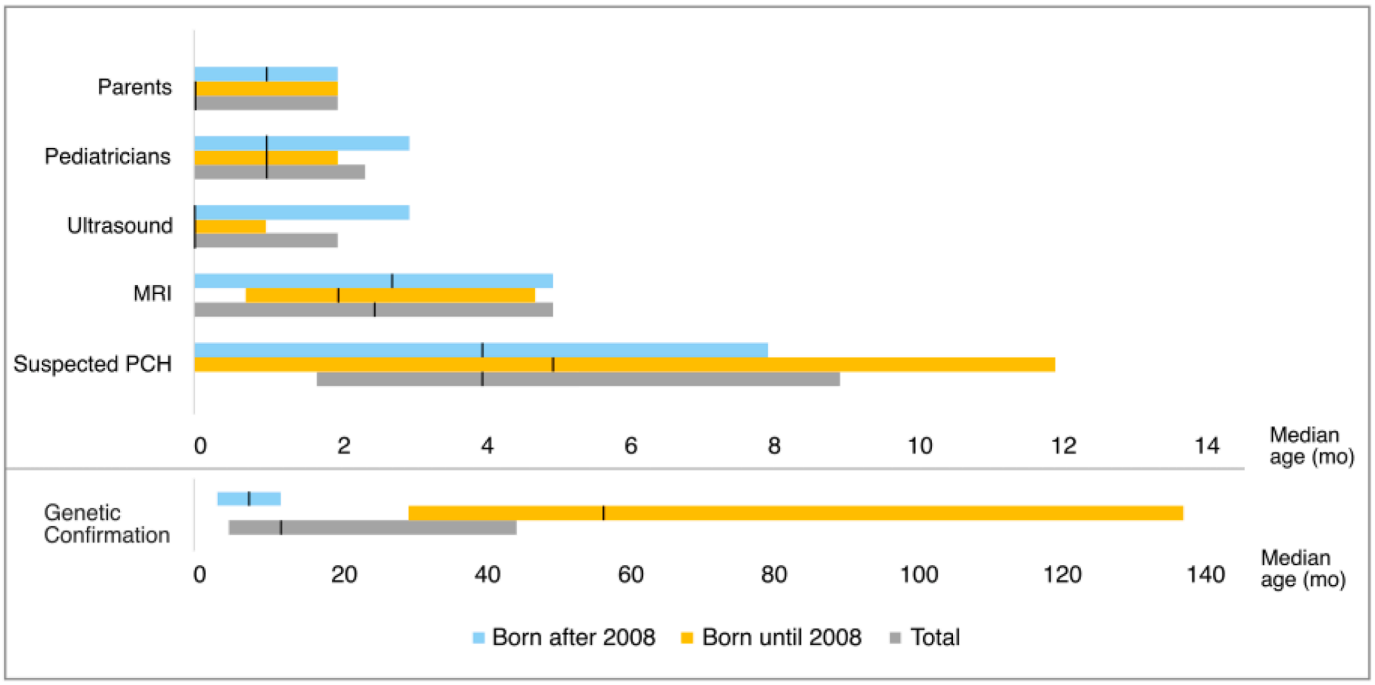

FIGURE 5. Timeline of diagnostic steps. Presentation of the various diagnostic steps from the first clinical abnormalities for the parents and pediatricians to the first ultrasound diagnosis, the first MRI and the expressed suspicion of PCH through to genetic confirmation. The median age of the children in months (black line) and the 25%- and 75%-quantiles (bars) are shown, without including outliers in the illustration. A different scale was used for genetic confirmation (bottom). The color coding stands for the two groups separated by the year of birth up to and including 2008 (orange) and after 2008 (blue). The total cohort is represented in gray. MRI = magnetic resonance imaging; PCH = pontocerebellar hypoplasia.

Postnatal imaging in PCH2A

Neurosonography is typically the first-line imaging modality in infants presenting with neurological concerns and was performed in the majority of our cases.[26-28] However, due to its limited ability to adequately visualize infratentorial structures, many findings remained vague or were misinterpreted, with terms such as "enlarged cisterna magna" frequently used. These limitations are consistent with previous reports.[17]

Progressive microcephaly in patients with PCH2A typically emerges during infancy.[10,11] In line with this, early closure of the anterior fontanelle was frequently observed in our cohort, likely reflecting impaired cerebral growth. This further restricted the acoustic window for ultrasound, complicating evaluation of posterior fossa structures.[29,30]

When cerebellar abnormalities are suspected, MRI is the modality of choice.[26,28] In our study, nearly all children underwent brain MRI, with 92% demonstrating abnormal findings. However, interpretation was not always accurate. In two cases—including one preterm infant—initial MRI reports failed to detect cerebellar abnormalities, which only became apparent on follow-up scans. This suggests that in some cases, initial cerebellar changes are too subtle for early detection, reinforcing the value of serial imaging or quantification methods.[2,3,10,16]

Additional imaging findings included ventriculomegaly, callosal hypoplasia, delayed myelination, and reduced brain volume—none of which are specific for PCH2A.[1,7,14] The Evans index was abnormal in all children older than 6.5 months, suggesting disproportionate ventricular enlargement.[16] Notably, Dandy–Walker malformation was suspected in five children, particularly in cases evaluated before 2008. This misinterpretation likely reflects limited awareness of PCH2A imaging features at the time and underscores the need for genetic confirmation when infratentorial abnormalities are identified.

TABLE 2.
Median Age at Diagnostic Milestones

	Median Age in Months (Range)		
	Total (N = 65)	Born Until 2008 (n = 30)	Born After 2008 (n = 35)
Clinical abnormalities first observed by parents	0 (0-6)	0 (0-3.5)	1 (0-6)
Clinical abnormalities first observed by pediatrician	1 (0-6)	1 (0-6)	1 (0-6)
First ultrasound	0 (0-12)	0 (0-12)	0 (0-5)
First MRI	2.5 (0-146)	2 (0-146)	2.75 (0-24)
Suspected PCH	4 (0-364)	5 (0-364)	4 (0-48)
Genetic confirmation	12 (0-364)	57 (4-364)	8 (0-50)
Time interval between symptom onset and genetic diagnosis	10 (0-364)	55.5 (2-364)	5 (0-148)

Abbreviations:
MRI = Magnetic resonance imaging
PCH = Pontocerebellar hypoplasia

Clinical indicators and time to diagnosis

Symptoms of PCH2A typically emerge in the neonatal period.[2,3,7] While some mothers retrospectively reported abnormalities already during pregnancy, these were often nonspecific. Most deliveries were uneventful; perinatal complications are more typical of more severe PCH types, such as PCH4 or PCH5.[2,14] Early progressive microcephaly is a key diagnostic clue of PCH2A.[3,11,15] Additional neurological abnormalities, such as altered tone with dyskinetic movements, feeding difficulties due to dysphagia, or persistent restlessness—should prompt further diagnostics in these infants.

In our cohort, the typical diagnostic sequence began with nonspecific symptoms in the first month, followed by neuroimaging at 2-3 months. A suspected diagnosis of PCH was usually reached within 6 months, with genetic confirmation around 12 months. For children born before 2008, diagnosis relied on clinical and radiological findings and was often delayed. Since then, time to diagnosis has decreased substantially. This underscores the value of early genetic testing in guiding care and family planning.[31] Although earlier diagnosis substantially shortened the time to genetic confirmation, this study did not systematically assess its impact on life expectancy or quality of life. Given the absence of disease-modifying treatment options for PCH2A yet, earlier diagnosis may still facilitate anticipatory care, supportive management, and informed family counseling.

Strengths and limitations

This study benefits from a relatively large cohort of genetically confirmed PCH2A cases, which is considerable given the rarity of the disorder. The comprehensive collection of detailed clinical and imaging data allows for an in-depth phenotypic characterization of early clinical features and diagnostic steps. Additionally, the inclusion of a subgroup analysis comparing patients born before and after 2008—the year when the genetic basis of PCH2A was identified—provides valuable insight into changes in diagnostic practices and highlights improvements in time to diagnosis.

However, several limitations must be acknowledged. The retrospective design inevitably leads to variability in data quality, including inconsistencies in medical documentation and questionnaire detail. Recall bias is particularly relevant, especially for older children, as parents may have difficulty accurately recalling early-life symptoms and events. Furthermore, the presence of previously diagnosed index cases in families with multiple affected children likely facilitated earlier recognition and diagnosis in younger siblings, introducing a potential ascertainment bias.

Other limitations include the predominantly European origin of our cohort, which may limit the generalizability of the findings to other populations. Prenatal findings may be under-reported due to limited availability and use of advanced imaging and genetic testing in earlier years. Additionally, imaging protocols were not standardized across centers, possibly affecting the consistency of findings.

Conclusions

Our findings highlight the diagnostic challenges of PCH2A, especially in the prenatal setting. Infratentorial abnormalities likely begin prenatally and may be visualized by MRI in late gestation; however, they are often subtle and can remain unrecognized when imaging is done early during gestation. In such cases, even mild cerebellar deviations should prompt consideration of a severe neurodevelopmental disorder such as PCH2A. Increased awareness of abnormal cerebellar trajectories in the third trimester, combined with careful imaging evaluation and genetic testing in families with a known risk, could substantially improve early detection and support informed reproductive planning.

Postnatally, affected children typically present with a distinct constellation of neurological symptoms. Brain MRI frequently reveals characteristic pontocerebellar abnormalities that can guide targeted genetic testing. Improved awareness of early clinical signs and imaging features can facilitate timely diagnosis, enable earlier genetic counseling, and support informed reproductive choices in at-risk families.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to improve the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Data availability

All data referenced in the manuscript are available upon request.

CRediT authorship contribution statement

Antonia Herrmann: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Alice Kuhn:** Formal analysis, Data curation. **Maren Hackenberg:** Validation, Methodology. **Julia Matilainen:** Project administration, Funding acquisition. **Simone Mayer:** Project administration, Funding acquisition. **Samuel Groeschel:** Project administration, Funding acquisition. **Markus Uhl:** Supervision. **Ingeborg Krägeloh-Mann:** Project administration, Funding acquisition. **Wibke G. Janzarik:** Writing – review & editing, Supervision, Conceptualization.

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