European Journal of Paediatric Neurology 56 (2025) 58–66

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

journal homepage: www.journals.elsevier.com/european-journal-of-paediatric-neurology

Original article

Brain morphometry and psychomotor development in children with PCH2A

Pablo Pretzel [b,c,*], Antonia Herrmann [a,1], Alice Kuhn [a], Anna-Lena Klauser [a], Julia Matilainen [d], Elias Kellner [e], Maren Hackenberg [f], Simone Mayer [g,h], Lucia Laugwitz [i], Markus Uhl [j], Samuel Groeschel [b,i], Wibke G. Janzarik [a]

[a] Department of Neuropediatrics and Muscle Disorders, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[b] Experimental Pediatric Neuroimaging, Department of Child Neurology and Department of Neuroradiology, University Hospital, Tübingen, Germany
[c] Department of Diagnostic and Interventional Neuroradiology, School of Medicine and Health, TUM Klinikum Rechts der Isar, Technical Universtiy of Munich, Germany
[d] German PCH Patient Network (PCH-Familie e.V.), Germany
[e] Medical Physics, Department of Diagnostic and Interventional Radiology, University Medical Center Freiburg, University of Freiburg, Germany
[f] Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Germany
[g] Hertie Institute for Clinical Brain Research, University of Tübingen, Germany
[h] Karlsruhe Institute of Technology, Zoological Institute and Institute of Biological and Chemical Systems – Functional Molecular Systems, Karlsruhe, Germany
[i] Department of Child Neurology and Developmental Medicine, University Children's Hospital, Tübingen, Germany
[j] Division of Pediatric Radiology, Department of Radiology, University Medical Center Freiburg, University of Freiburg, Freiburg, Germany

ARTICLE INFO

Keywords:
Pontocerebellar hypoplasia type 2A
Long-term brain morphometry
Developmental phenotype
Progressive microcephaly
Delayed psychomotor development

ABSTRACT

Introduction: Pontocerebellar hypoplasia type 2A (PCH2A) is a rare neurogenetic disease characterized by severe cognitive and motor impairment. This study reports on brain morphometry and psychomotor development of affected children.

Materials and methods: We analyzed 78 cerebral MRI datasets of 57 patients with genetically confirmed PCH2A. Volumetric and in-plane measurements were conducted in cerebellum, neocortex and pons. Supratentorial width and width of the anterior horns of the lateral ventricles was used to calculate the Evans index. Caregivers of 65 patients (aged 7 months to 33 years) filled in a survey assessing motor and cognitive development. Developmental status was compared to MRI measurements.

Results: In children with PCH2A, cerebellar volume was markedly smaller than in healthy children at birth, with slower increase and stagnation at around 12 months. No cerebellar growth was observed in the cranio-caudal axis. Longitudinal data did not reveal a decrease in cerebellar volume or in-plane measurements. Supratentorial measurements showed progressive microcephaly and a continuous increase of the Evans index, reflecting progressive cerebral atrophy. Patients demonstrated severe cognitive and motor impairments, with developmental regression reported in only a minority. No statistical relationship between brain measurements and cognitive or motor development was observed.

Conclusion: MRI in PCH2A patients shows limited cerebellar growth during infancy, especially restricted along the cranio-caudal axis. After infancy, cerebellar volume remains relatively stable. Supratentorial measurements indicate slowly progressive atrophy. Psychomotor development is significantly impaired, but regression is rare.

1. Introduction

Pontocerebellar hypoplasia (PCH) is a group of very rare, autosomal recessive genetic diseases. This study focuses on PCH type 2A (PCH2A), the most common subtype [1]. This subtype is defined by a homozygous pathogenic variant p.A307S (c.919G > T) in the *TSEN54* gene, which is thought to result in impaired tRNA processing [2,3], and potentially, mRNA decay [4,5].

Children with PCH2A exhibit early-onset symptoms, such as impaired swallowing, restlessness, and a choreatic movement disorder. Additional neurological symptoms, such as long-lasting dystonic attacks, spasticity, and epileptic seizures, often develop within the first years of life [6]. Both motor and cognitive development are severely

* Corresponding author. Experimental Pediatric Neuroimaging, Department of Child Neurology and Department of Neuroradiology, University Hospital, Tübingen, Germany.
E-mail address: pablo.pretzel@med.uni-tuebingen.de (P. Pretzel).
[1] Shared first authorship.

https://doi.org/10.1016/j.ejpn.2025.04.004
Received 8 December 2024; Received in revised form 25 March 2025; Accepted 9 April 2025
Available online 15 April 2025

Abbreviations

CI	Confidence Interval
ICC	Intraclass Correlation Coefficient
LOESS	Local Estimated Scatterplot Smoothing
mRNA	messenger RNA
PCH	Pontocerebellar hypoplasia
PCH2A	Pontocerebellar hypoplasia type 2A
tRNA	transfer RNA

compromised. All children with PCH2A present with severe progressive microcephaly [7]. Life expectancy is limited, with many affected individuals dying during childhood and adolescence [1,6,7].

Neuroimaging of children with PCH2A reveals characteristic severe hypoplasia of pons and cerebellum, with a relative sparing of the cerebellar vermis, resulting in the characteristic "dragonfly pattern" [8]. Histological findings indicate loss of cerebellar cortex, fragmentation of the dentate nuclei, and near absence of transverse pontine fibers [1,9]. Supratentorial structures are also affected, with reduced cerebral volume and enlarged ventricles [10].

However, due to the rarity of PCH2A, little data is available on the detailed longitudinal trajectory of brain measurements of affected children before and beyond the first year of life. Only a small number of prior studies provided cross-sectional data, mainly from the first months of life: Van Dijk et al [11] reported on 18 patients aged 14.8 months or younger, Ekert et al [10] reported on 24 children aged 17 years or less (median 10 months).

In the present study, we aimed to expand the understanding of the brain structural phenotype and developmental phenotype of PCH2A by investigating a larger cohort, with data including repeated MRI and MRI of older patients. Specifically, this approach would allow to characterize the long-term trajectory of the disease and assess whether progressive developmental regression or cerebral atrophy occur with increasing age. A comprehensive characterization of the course of PCH2A will benefit clinicians, researchers, and affected families.

2. Materials & methods

Patients with PCH2A were recruited through the German patient organization PCH-Familie e.V., and data from the first natural history study were included [6]. Inclusion criteria required genetic confirmation of the homozygous pathogenic variant p.A307S in the *TSEN54* gene and written informed consent from the legal guardian. The study was approved by the ethics committee of the University of Freiburg, Germany (decision no. 20–1040) and by the ethics committee of the University of Tübingen (decision no. 105/2012BO2), as part of a natural history study on patients with PCH2A.

Parents completed a disease-specific survey providing data on motor and cognitive development. Additionally, imaging data and medical records were collected for a retrospective analysis when available. In some cases, parents did not complete the survey but provided consent for the use of MRI data in the analysis.

2.1. Brain morphometry

In MRI datasets with sufficient quality (effective slice thickness ≤ 3 mm, and a field of view covering the entire brain), the volumes of the cerebellum, pons, supratentorial structures, and ventricles were measured by manually delineating the respective structures and calculating the volume of the generated masks (see Supplementary Fig. 1). Additionally, in-plane measurements of specific brain structures were performed in all MRI datasets with an appropriate field of view (see Supplementary Fig. 2): Infratentorial measurements included the cerebellar transverse diameter, anterior-posterior length, superior-inferior height (averaged between left and right lobe), and the midline anterior-posterior diameter of the pons. Supratentorial measurements included the maximum transverse diameter of the anterior horns of the lateral ventricles, and the transverse diameter of the cerebrum in the same axial plane. From these, the Evans index was calculated to evaluate supratentorial brain atrophy [13]. All in-plane measurements were conducted using DeepUnity (Dedalus Healthcare Group, Bonn, Germany), and volumetric masks were created using Nora (nora-imaging.com).

Reference data of cerebellar and cerebral volume were derived from a previous study using a similar methodological approach [10]. Reference data of pontine diameter were obtained from the literature [12]. To assess the reliability of the measurements performed by the first rater (AH), both in-plane and volumetric measurements were independently repeated in 34 and 10 randomly selected datasets, respectively, by a second researcher (PP), who was blinded to the original results. Inter-rater variability was assessed using the Intraclass Correlation Coefficient [13]. Statistical analyses were carried out using SPSS (IBM, Armonk, NY) and R [14] with visualizations produced using SPSS and ggplot [15].

2.2. Assessment and classification of psychomotor development

As part of the parent survey, the developmental history of the participating patients with PHC2A was assessed across various motor and cognitive skills, as described in a previous publication [6]. For each skill, parents were asked whether and at what age their child had achieved the skill, and whether development of this skill was still ongoing, or at what age the development had plateaued. Additionally, parents were asked whether their child demonstrated the skill consistently or intermittently, and whether the child had lost the skill at any point.

The developmental data were retrospectively collected from 65 children with PCH2A, of whom 21 had previously participated in the earlier Natural History Study (NHS) conducted in 2014. Among this subgroup, parents were provided with the option to reference their previous questionnaire or, in some cases (6), a pre-filled version was sent to aid with recall. Discrepancies between parental reports and medical records were addressed in follow-up telephone interviews, which were conducted for all participants to enhance the accuracy of the data. In rare cases of persistent disagreement between parental assessments and documented findings, we accepted the parental assessment due to their continuous observation of the child.

To categorize the variability of psychomotor development among children with PCH2A, we calculated the median age of skill acquisition for each skill among all children who had demonstrated it. Based on these cohort-specific development timelines, we determined the ratio of skills achieved by each child relative to those typically achieved by children with PCH2A at the same age. The top 15 % of children with the highest ratio were classified as having above-average development, while the bottom 15 % were classified as having below-average development. The remaining children were classified as having average development. We then compared cerebellar and supratentorial measurements with these developmental classifications.

3. Results

Cohort details are listed in Table 1. From 17 patients, two imaging datasets were available, and from 2 patients, three longitudinal data points were available.

3.1. Volumetric measurements

Results of the volumetric measurements are presented in Fig. 1. At birth, a significant difference in cerebellar volume was already apparent between children with PCH2A and healthy controls (Fig. 1, upper left).

Table 1
Cohort details.

Total enrolled patients	72
Patients with available MRI	57
Total available MRI datasets	78
MRI acquired in utero	3
MRI datasets suitable for volumetry (effective slice thickness ≤ 3 mm)	48
Gender of patients with available MRI	33 female (58 %), 24 male (42 %)
Median age at MRI	4,5 months (31 weeks of gestation – 18.7 years)
Patients with developmental data	65
Gender of patients with developmental data	33 female (51 %), 32 male (49 %)
Median age at time of the survey	6,3 years (7 months – 33 years)

Patients exhibited limited cerebellar growth during the first months of life, after which the interpolated logarithmic growth curve progressively flattened and eventually plateaued at a volume of approximately 20 ml (upper right). Healthy controls showed a markedly faster and ongoing cerebellar growth. There was no observed difference between male and female patients.

Differences in supratentorial brain volume were less pronounced at birth with patients showing only a moderate lag compared to healthy controls during the first few months of life (Fig. 1, bottom left). However, after the first year, supratentorial cerebral growth also stagnated in patients with PCH2A, leading to persistently lower volumes compared to healthy controls (bottom right). No sex-based differences were observed.

Neither cerebellar nor supratentorial volumes showed progressive volume loss in individual data points or longitudinal follow-up data. The qualitative analysis of individual follow-up data support the trends observed in the cohort. This is demonstrated in Fig. 1, where dashed lines connect data points from the same children indicating that morphometric changes closely follow the interpolated logarithmic growth curves.

3.2. Measurements of cerebellar and pontine diameters over time

Cerebellar and pontine diameter measurement complement the volumetric data (Fig. 2). The growth curves for cerebellar transverse diameter (top row) and anterior-posterior diameter of the cerebellum (second row) show a similar pattern to cerebellar volumetry, with patients exhibiting initial growth during the first months of life, but with slower progress and earlier stagnation compared to healthy controls. A similar pattern is observed in the pontine anterior-posterior diameter (bottom row). However, the cranio-caudal diameter of the cerebellar hemispheres remains relatively stable after birth, showing no growth either during infancy or later developmental stages (Fig. 2, third row). In some children with follow-up MRI, we observed a slight decrease in cranio-caudal cerebellar diameter, particularly noticeable in one child whose diameter decreased from 9.5 mm immediately after birth to 3 mm at 8 months corrected age (see Supplementary Fig. 3). No significant sex-based differences were noted.

Qualitative inspection of the longitudinal MRI data from individual patients generally confirmed these trends, especially for transverse and anterior-posterior diameters, as illustrated in Fig. 2. However, two children deviated from this trend: one showed a reduction of approximately 7 mm in the cranio-caudal diameter between an MRI on postnatal day 1 (preterm, gestational age of 30 + 4 weeks) and at 9 months of age, while another child exhibited a slight decrease in this dimension at approximately 10 years of age (see Supplementary Fig. 3).

3.3. Measurements of supratentorial diameter over time

Supratentorial in-plane measurements are shown in Fig. 3.

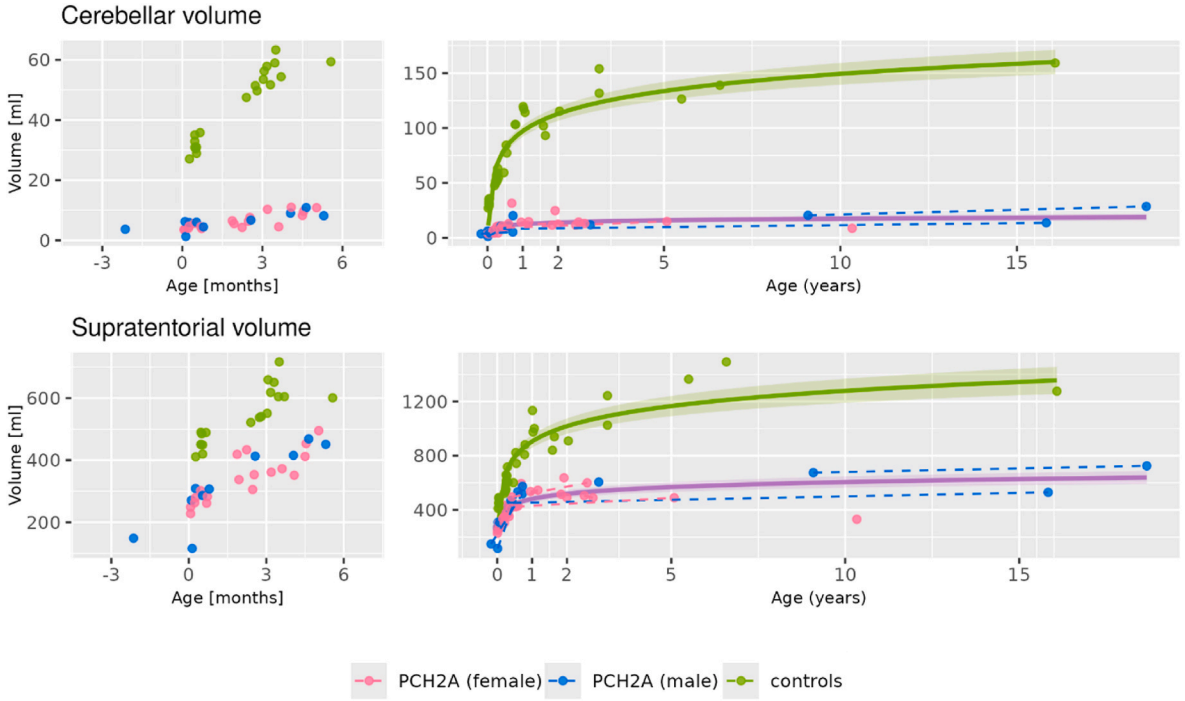

Fig. 1. Volumetry of the cerebellum (top) and supratentorial structures (bottom). Volumes of both structures show markedly decreased brain growth in children with PCH2A as compared to healthy controls. Growth restriction is more pronounced in the cerebellum than in supratentorial brain structures, especially during the first months of life (left). After the first year, brain volumes remain stable in patients with PCH2A, whereas healthy controls show continuous growth of brain structures during childhood (right). Measurements from longitudinal data of the same patients (dashed lines) fit to the interpolated logarithmic curve (solid line, lighter shade: 95 % confidence interval). Values on the left side of time point zero reflect prenatal MRI. No differences are observed between male and female patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

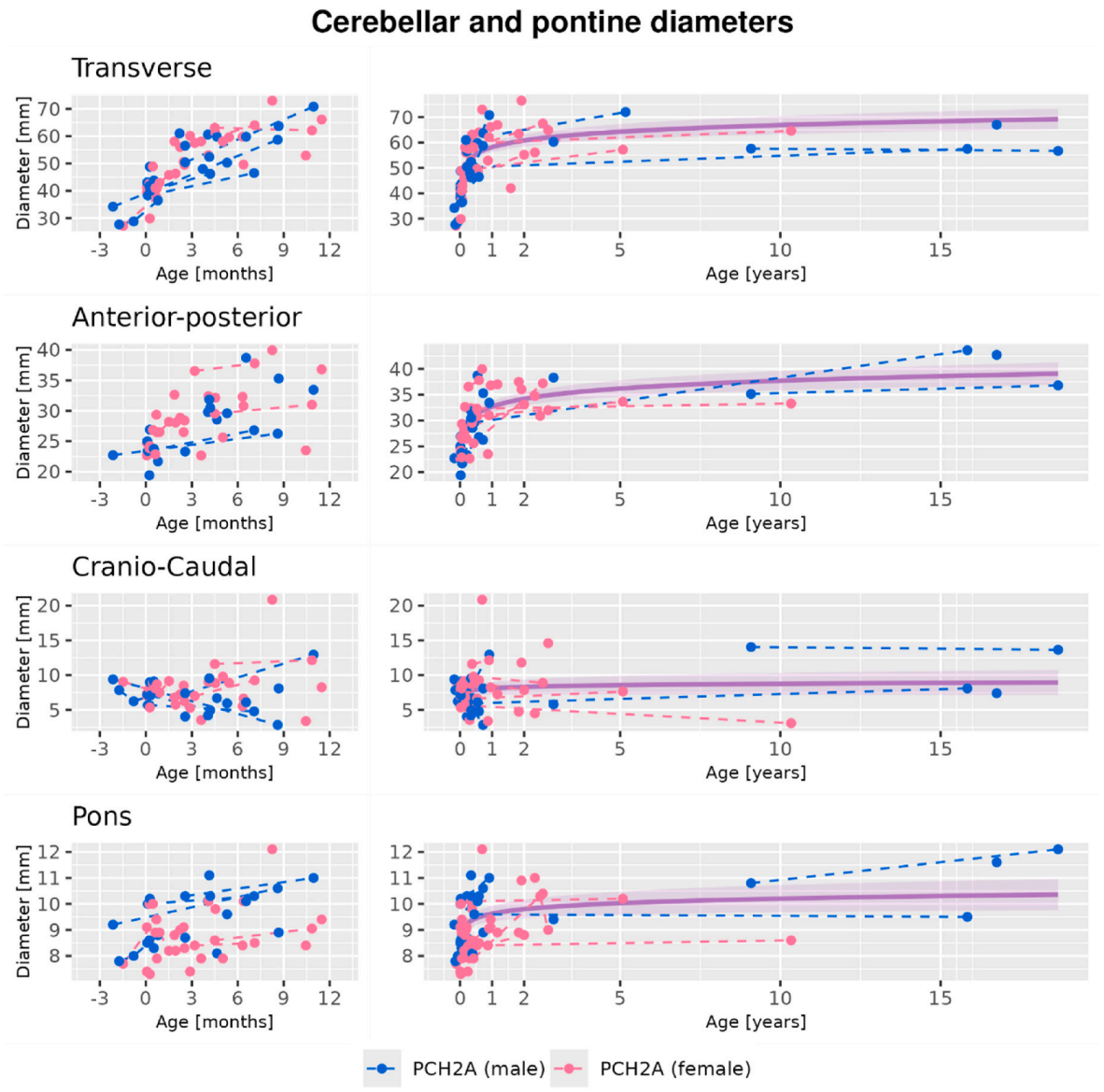

Fig. 2. Cerebellar measurements in transversal (top), anterior-posterior (second row) and cranio-caudal (third row) direction, as well as anterior-posterior pontine diameter (bottom row). Over the first year of life, cerebellar size increases in transverse diameter and anterior-posterior length, but not in cranio-caudal height (left). Together, this results in the characteristic dragonfly pattern commonly observed in PCH2A. After the first years of life, cerebellar growth ceases in all dimensions (right). Pontine diameter increases slightly in the first year of life, then also stagnates. Dashed lines indicate longitudinal data of the same patient and provide a good fit to the interpolated logarithmic curves (solid lines). No clear growth difference is observed between male and female patients. Values in the negative range reflect prenatal MRI (3 cases) or MRI of a premature child (1 case). See Supplementary Fig. 2 for an illustration.

Transverse cerebral width (top row) follows a similar growth and subsequent stagnation pattern as cerebellar structures, but at a later developmental stage. Simultaneously, the width of the lateral ventricles shows a continuous increase (middle row). Together, these trends lead to a progressive increase in the Evans index (bottom row), which surpasses the threshold of 0.3, defined as the upper limit for healthy controls regardless of age [16], shortly after birth. No MRI scans showed signs of elevated intracranial pressure or cerebrospinal fluid circulation obstruction.

3.4. Inter-rater correlation

The intraclass correlation coefficient (ICC) for the volumetric measurements was 0.97 for cerebellar volumes (95%confidence-interval [CI] 0.88–0.99) and 0.991 for supratentorial volumes (95% CI 0.67–1.0). For two-dimensional diameters, the ICC ranged from 0.92 to 0.97 for cerebellar diameters (CI 0.82–0.96 and 0.93–0.98), and was 0.86 for pontine diameters (CI 0.71–0.94). The ICC for supratentorial measurements was 0.94 (CI 0.88–0.97) for cerebral diameter and 0.99 for lateral ventricle diameter (CI 0.97–0.99).

3.5. Psychomotor development

Motor skill development is illustrated in Fig. 4 (top). A significant number of children achieved basic motor skills, such as head control (68% of children older than the median age at which the skill was typically achieved) or grasping attempts (74%). Rolling over and targeted grasping was learned by 52% and 40%, respectively. More advanced motor skills, however, were rarely achieved (crawling: 16%, on all fours: 12%, unsupported sitting: 9%). All motor skills were acquired with significant delay compared to healthy children, and 10 children were reported to have never learned any of the queried motor

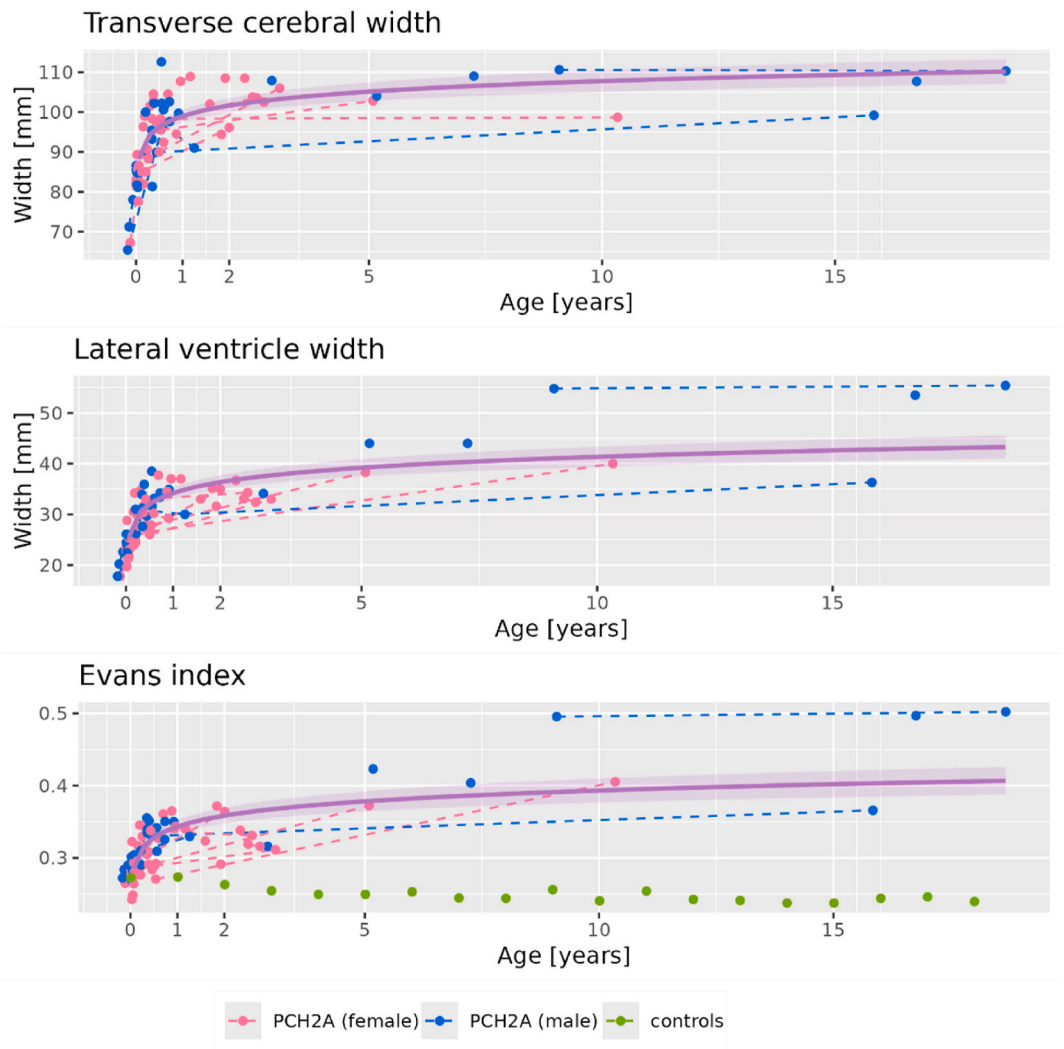

Fig. 3. Supratentorial measurements: Transverse cerebral width (top), width of the anterior horns of the lateral ventricles (middle), Evans index (bottom). While transverse cerebral width stagnates around the age of 12 months, similar to infratentorial measures, the width of the anterior horns of the lateral ventricles continues to increase, causing the Evan's index to rise above the threshold of 0.3 established for healthy children.

skills. For all motor skills, at least one child was reported to have lost the skill after acquisition (grasping attempts and rolling over: 5 children each, all other skills: 1–2 children each).

Regarding cognitive development (Fig. 4, bottom), parents reported that their child consistently responded to familiar people or objects (94%), exhibited a social smile (88%), and reacted to visual stimuli (85%). Controlled eye movements were also reported by the majority of parents (reaction to visual stimuli: 94%, fixation: 88%, eye tracking: 81%). However, reproducible communication by specific sounds or words was less common (53% and 17%, respectively). Only a small number of children were reported to have lost skills (eye tracking and specific sounds: 2 each, fixation, social smile and specific words: 1 each). All skills were acquired considerably later than in healthy children.

3.6. *Relationship between psychomotor development and imaging findings*

No clear correlation was found between psychomotor development, categorized as "below average," "average," or "above average," and brain measurements (Fig. 5). Most children with below-average psychomotor development had transverse cerebral diameters below the interpolated growth curve (Fig. 5, bottom right). Conversely, children with above-average development in both motor and cognitive domains generally had cerebellar diameters above the interpolated growth curve (upper and lower left). No further associations between cerebral measurements and motor skills were observed (data not shown).

4. Discussion

We analyzed brain measurements from the prenatal period into adolescence, as well as psychomotor development, in a large cohort of children with PCH2A, broadening our understanding of the imaging and clinical phenotype of this genetically homogenous group.

4.1. *Growth is highly limited in both supra- and infratentorial regions*

Volumetic analysis (Fig. 1) shows reduced cerebellar ad supratentorial volumes already at birth, with cerebellar reductions to be more pronounced. This aligns with findings from a recent PCH2A organoid model [17]. While healthy children show significant brain growth postnatally, PCH2A patients exhibit severe growth restriction in both supra- and infratentorial structures, leading to progressive microcephaly and severe cerebellar hypoplasia. Our data support the clinical observation that early postnatal ultrasounds in affected children often show abnormalities primarily in the cerebellum (frequently described as an enlarged cisterna magna), while most children are still normocephalic at birth [6].

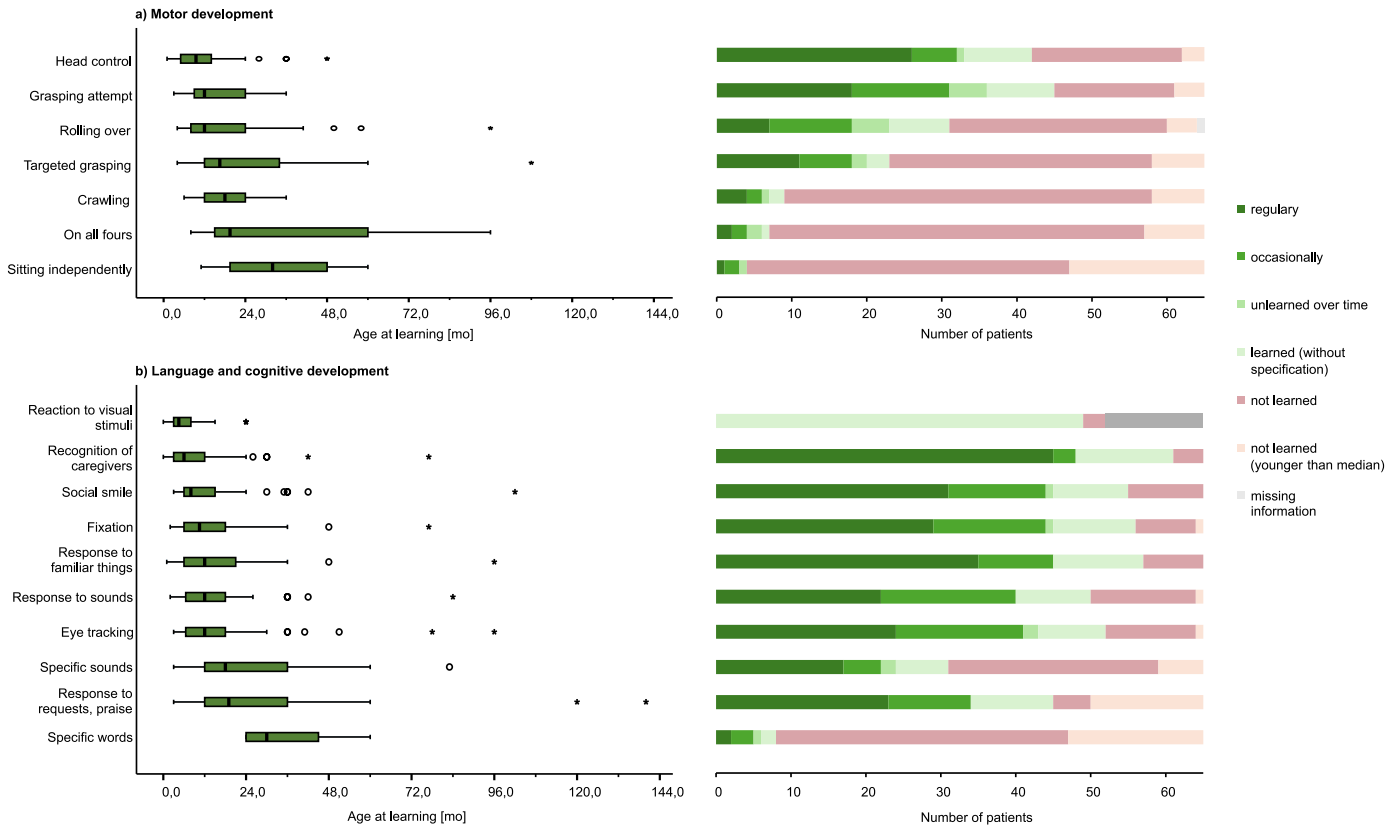

Fig. 4. Motor development (top) and language and cognitive development (bottom) of children with PCH2A, as reported by caregivers. Left side: Age at which the skill was first demonstrated. Right side: Absolute number of children that achieved, unlearned or never achieved the respective skill. Total green bar: Number of children that ever achieved the skill. Individual shades of green differentiate the frequency with which the skill was demonstrated. Red bar: Number of children that never achieved the skill. Light orange: Children who were younger at the time of assessment than the median age at which the skill was achieved by children with PCH2A.
Motor development (top): Simpler skills like head control, turning and grasping attempts were demonstrated by about half the children, mostly within the first few years of life, but considerably later than in healthy children. More complex abilities were only demonstrated by a small number of children, and at a higher and more widely distributed age. For each skill, several parents reported that their child had achieved the skill at some point but did not exhibit it anymore.
Cognitive development (bottom): A considerable number of children started to exhibit nonverbal communication within the first two years of life, such as limited eye movement and reproducible reactions to familiar people and objects. Reproducible verbal communication (sounds or specific words) was reported only for few older children. Overall, as reported by their caregivers, the queried cognitive skills are achieved by a significantly higher number of children than the queried motor skills, and only very few children are reported having unlearned a skill. No data on frequency was available for reaction to visual stimuli. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4.2. Cerebellar growth is affected in a spatial manner

Cerebellar growth in children with PCH2A is spatially variable (Fig. 2). Specifically, our measurements of the cerebellum of affected children show an increase in width and length during the first two years, but not in height, which results in the characteristic dragonfly pattern. While cranio-caudal height decreased in a few children, the transverse and anterior-posterior diameters remained stable. Histopathology shows both extensive dysplasia and atrophy of cerebellar neurons and axons [9]. In cranio-caudal direction, these processes might be balanced by early growth and could result in an apparently stable situation over time. Alternatively, cerebellar growth might be inhibited in cranio-caudal direction right from the beginning. In the further course of the disease, processes of growth and degeneration result in a net stable cerebellar volume in older PCH2A patients without signs of progressive degeneration. Histopathological findings suggest that the remaining cerebellar tissue might in large parts be gliotic, rather than functional cerebellar tissue [9].

4.3. Progressive supratentorial atrophy

In contrast, supratentorial atrophy progresses over time. The Evans index exceeds healthy thresholds in early infancy [16], continuing to rise in the absence of hydrocephalus (Fig. 3). This indicates ventriculomegaly due to cerebral atrophy rather than increased intracranial pressure. Histological findings in the neocortex of PCH2A patients show a diffuse increase in glial tissue without active degeneration, and both cortical architecture as well as myelination of axonal tissue appeared normal even in atrophic regions [9].

In PCH2A, supratentorial atrophy takes place in a different temporal manner than cerebellar atrophy, i.e. initially less rapid, but as an ongoing process over time. Supratentorial atrophy may be secondary to disrupted cerebro-cerebellar connections rather than a primary genetic effect [10]. However, neocortical organoids derived from patients with PCH2A showed delayed growth restriction as compared to cerebellar organoids without significant signs of apoptosis in either cerebellar or neocortical organoids [17]. The growth restriction of neocortical organoids was thus neither caused by cerebellar processes nor by predominant neurodegeneration but could be a direct effect of the genetic alteration in neocortical cells. Future studies might investigate both the longitudinal neocortical neuropathology, as well as cerebro-cerebellar connections, to resolve this debate.

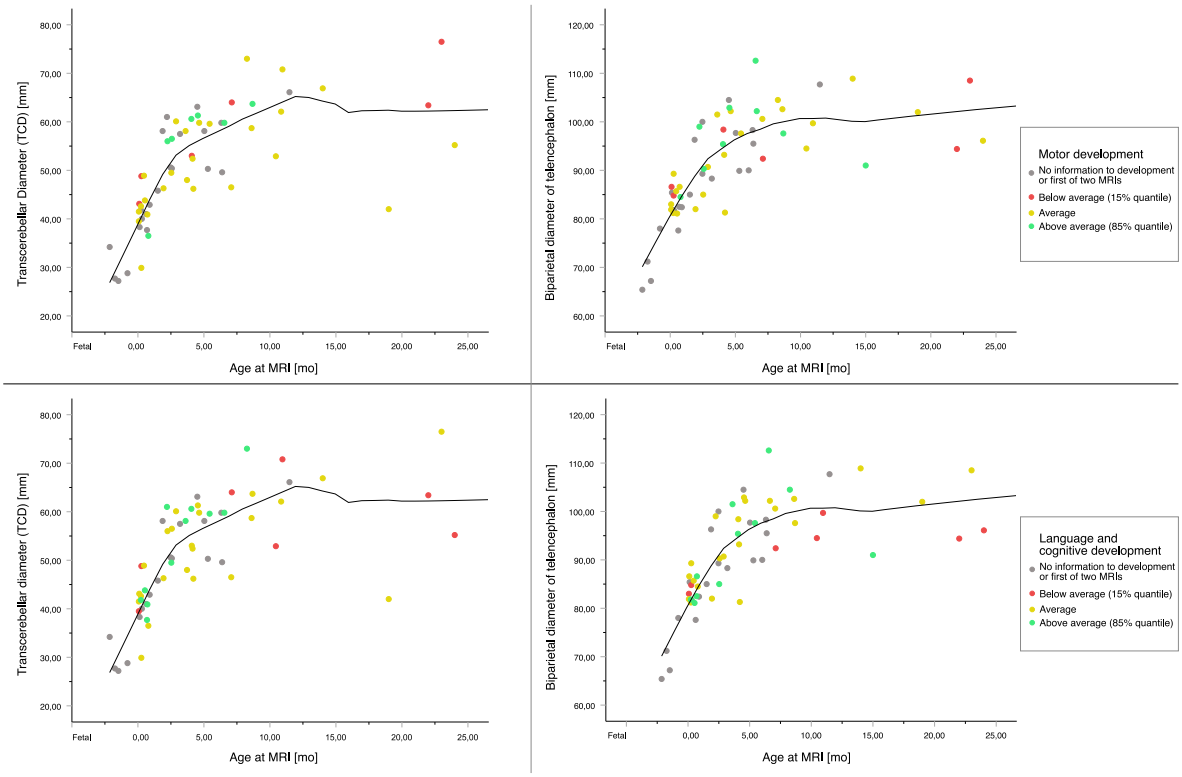

Fig. 5. Relation of motor (upper row) and cognitive (bottom row) development with transversal diameter of the cerebellum (left) and cerebrum (right) during the first two years of life. Colors denote the classification of patients into below-average development (red), normal development (yellow) and above-average development (green). Interpolated using local estimated scatterplot smoothing (LOESS). Lower transverse cerebral diameter appears to be associated with poorer cognitive development (lower right panel), while the remaining data do not suggest meaningful correlation between brain measurements and cognitive development. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4.4. Analysis of individual follow-up data

Longitudinal data from 19 patients, though too heterogeneous for quantitative analysis, allowed qualitative assessment and closely mirrored cohort trends. One notable exception was a reduction in cranio-caudal cerebellar diameter in two children, suggesting possible regional differences in degeneration over time.

4.5. Psychomotor development

Motor development (Fig. 4, top) was severely delayed in all patients. Few children achieved head control, grasping, or rolling over, while cognitive skills were reported in a slightly larger number (Fig. 4, bottom). This observation corroborates clinical experience, where caregivers are frequently able to interact with their child to a certain degree, and children with PCH2A might appear limited in their expression of cognitive abilities by their motor impairments. However, these observations are based on qualitative comparisons from questionnaire data, as our data collection did not allow for standardized testing or quantitative analysis of developmental and motor scores.

On one hand, pronounced cerebellar pathology likely contributes to motor dysfunction, given the cerebellum's role in controlling and coordinating muscle activity. On the other hand, the observed discrepancy between motor and cognitive abilities in patients with PCH2A may be influenced by the questionnaire design, which assessed simpler cognitive skills, while the motor tasks required a higher level of coordination. Potential parental bias in the assessment of their child's cognitive abilities must also be considered. Despite histological evidence for neurodegeneration [9], some developmental progress is achieved by all patients with PCH2A. Developmental regression is rare once a skill has been acquired, and the small discrepancies between the number of unlearned motor and cognitive skills do not provide sufficient evidence to draw conclusions about whether these regressions are due to neurodegeneration or other factors, such as body growth during adolescence.

We found no clear correlation between brain morphometry and developmental outcomes. In addition to its well-known motor functions, the cerebellum has been reported to be involved in cognitive processes, and cerebellar dysfunction has been linked to cognitive impairment [18–20]. At the same time, the genetic defect underlying PCH2A might also affect supratentorial networks involved in both motor and cognitive development, as well as cerebro-cerebellar connections. Further studies, with more detailed imaging and network analyses, are needed to clarify the contributions of cerebellar and cerebral pathology in this condition.

4.6. Limitations

This study has several limitations, particularly regarding the developmental data, which were primarily based on caregiver reports. Since standardized testing was unavailable, both motor and cognitive milestones were assessed through parental observations. It should be noted that the developmental trajectories of children with PCH2A do not correspond to those of typically developing children. For instance, head control is less stable, purposeful grasping requires significant effort, is often atactic, and can only be sustained for brief periods. Complex motor tasks, such as independent tooth brushing, are typically not achievable. Visual tracking is slowed and grossly saccadic, deviating from the smooth pursuit seen in healthy development. Similarly, cognitive abilities may only be observed sporadically, particularly during moments of well-being or in interactions with familiar individuals and may not be fully captured during clinical examinations. While caregiver reports are a valuable source of information, there is a potential for bias in their perception of their child's abilities. However, these observations are

consistent with broader clinical experience in PCH2A.

The developmental data were gathered retrospectively by asking parents about milestone achievements, which may introduce recall bias. This dataset included 21 children who had previously participated in the Natural History Study approximately 10 years ago [6]. While parents had the option to refer to previous questionnaires or prefilled data (used in 6 cases), discrepancies in reporting long-past milestones may exist, introducing further bias. This limitation applies specifically to the 16 patients who participated in both studies, as 5 had already passed away by 2012, which limits the ability to draw meaningful conclusions from longitudinal data for these cases.

Additionally, clinical and imaging data were not collected concurrently. The parental surveys were completed between 2020 and 2022, whereas the imaging data were analyzed retrospectively, with MRI scans often performed years earlier. In older children, MRI findings may not reflect the current developmental status at the time of the survey, limiting the ability to correlate imaging results with developmental progress. However, this does not affect the separate analyses of MRI metrics and psychomotor development. Furthermore, early brain MRI cannot reliably predict individual developmental outcomes.

5. Conclusion

This study provides comprehensive data on intracranial brain growth and psychomotor development from the prenatal period through adolescence in a large cohort of children with PCH2A. Affected children had a smaller cerebellum at birth, with the gap widening over the first year and then stagnating. Long-term data showed no cerebellar volume loss in older children, but progressive supratentorial atrophy and microcephaly were observed. Caregivers reported cognitive development in most children, though motor and cognitive skills were severely delayed. Developmental regression was rare. This study expands current knowledge of PCH2A and offers valuable insights for clinicians, researchers, and families.

Author contribution statement

AH: Data acquisition, analysis: interpretation, visualization, writing – review and editing, PP: Data analysis, interpretation, visualization, writing – original draft, writing – review and editing, AK: data acquisition, data interpretation, ALK: data acquisition, data interpretation, JM: Conceptualization, funding acquisition, data acquisition, writing – review and editing, EK: Data analysis (NORA), MH: statistical analysis, SM: Conceptualization, funding acquisition, writing – review and editing, LL: Conceptualization, data interpretation, MU: MRI, data analysis, SG: Conceptualization, funding acquisition, data interpretation, writing – review and editing, WJ: Conceptualization, funding acquisition, data acquisition, data interpretation, writing – review and editing, supervision.

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 clarity and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Funding

This project has been made possible in part by grant number 2022-316727 from the Chan Zuckerberg Initiative DAF, an advised fund of Silicon Valley Community Foundation.

This research has been partially funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy via the Excellence Cluster 3D Matter Made to Order (EXC-2082/1 – 390761711).

The work of MH is funded by the Deutsche Forschungsgemeinschaft (DFG,German Research Foundation) – Project-ID 499552394 – SFB 1597.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

Acknowledgements

We acknowledge the kind support of the patients' organization for German-speaking countries (PCH-Familie e.V.) in contacting the families of affected children.

We acknowledge support by Maximilian F Russe, Department of Diagnostic and Interventional Radiology, University Medical Center Freiburg, University of Freiburg, Freiburg, Germany.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2025.04.004.

References

[1] Sabine Rudnik-Schöneborn, Peter G. Barth, Klaus Zerres, Pontocerebellar hypoplasia, Am. J. Med. Genet. Part C: Seminars in Medical Genetics 166 (2) (2014) 173–183, https://doi.org/10.1002/ajmg.c.31403.

[2] Paul R. Kasher, Yasmin Namavar, Paula van Tijn, Kees Fluiter, Aleksander Sizarov, Maarten Kamermans, Andrew J. Grierson, Danica Zivkovic, Baas Frank, Impairment of the tRNA-splicing endonuclease subunit 54 (Tsen54) gene causes neurological abnormalities and larval death in zebrafish models of pontocerebellar hypoplasia, Hum. Mol. Genet. 20 (8) (April 15, 2011) 1574–1584, https://doi.org/10.1093/hmg/ddr034.

[3] Yasmin Namavar, Peter G. Barth, Paul R. Kasher, Fred van Ruissen, Knut Brockmann, Günther Bernert, Karin Writzl, et al., Clinical, neuroradiological and genetic findings in pontocerebellar hypoplasia, Brain: J. Neurol. 134 (Pt 1) (January 2011) 143–156, https://doi.org/10.1093/brain/awq287.

[4] Sergey V. Paushkin, Meenal Patel, Bansri S. Furia, Stuart W. Peltz, Christopher R. Trotta, Identification of a human endonuclease complex reveals a link between tRNA splicing and pre-mRNA 3′ end formation, Cell 117 (3) (April 2004) 311–321, https://doi.org/10.1016/S0092-8674(04)00342-3.

[5] Jennifer E. Hurtig, Michelle A. Steiger, Vinay K. Nagarajan, Tao Li, Ti-Chun Chao, Kuang-Lei Tsai, Ambro van Hoof, Comparative parallel analysis of RNA ends identifies mRNA substrates of a tRNA splicing endonuclease-initiated mRNA decay pathway, Proc. Natl. Acad. Sci. U. S. A 118 (10) (March 9, 2021) e2020429118, https://doi.org/10.1073/pnas.2020429118.

[6] Iciar Sánchez-Albisua, Saskia Frölich, Peter G. Barth, Maja Steinlin, Ingeborg Krägeloh-Mann, Natural course of pontocerebellar hypoplasia type 2A, Orphanet J. Rare Dis. 9 (May 5) (2014) 70, https://doi.org/10.1186/1750-1172-9-70.

[7] Alice Kuhn, Maren Hackenberg, Anna-Lena Klauser, Antonia Herrmann, Julia Matilainen, Simone Mayer, Saskia Frölich, Ingeborg Krägeloh-Mann, Samuel Groeschel, Wibke G. Janzarik, Growth charts for pontocerebellar hypoplasia type 2A, medRxiv (June 24, 2024), https://doi.org/10.1101/2024.06.23.24307757.

[8] Yasmin Namavar, Peter G. Barth, Bwee Tien Poll-The, Baas Frank, Classification, diagnosis and potential mechanisms in pontocerebellar hypoplasia, Orphanet J. Rare Dis. 6 (July 12, 2011) 50, https://doi.org/10.1186/1750-1172-6-50.

[9] Peter G. Barth, Eleonora Aronica, Linda de Vries, Peter G.J. Nikkels, Wiep Scheper, Jeroen J. Hoozemans, Dirk Troost, Bwe - Tien Poll-The, Pontocerebellar hypoplasia type 2: a neuropathological update, Acta Neuropathol. 114 (4) (October 2007) 373–386, https://doi.org/10.1007/s00401-007-0263-0.

[10] Kaspar Ekert, Samuel Groeschel, Iciar Sánchez-Albisua, Saskia Frölich, Andrea Dieckmann, Corinna Engel, Ingeborg Krägeloh-Mann, Brain morphometry in pontocerebellar hypoplasia type 2, Orphanet J. Rare Dis. 11 (1) (July 19, 2016) 100, https://doi.org/10.1186/s13023-016-0481-4.

[11] Tessa van Dijk, Peter Barth, Frank Baas, Liesbeth Reneman, Bwee Tien Poll-The, Postnatal brain growth patterns in pontocerebellar hypoplasia, Neuropediatrics 52 (3) (2021) 163–169, https://doi.org/10.1055/s-0040-1716900.

[12] Gabriel Promnitz, Joanna Schneider, Naomi Mohr, Birgit Spors, Angela M. Kaindl, Standard values for MRI brain biometry throughout the first year of life, Pediatrics & Neonatology 63 (3) (May 2022) 255–261, https://doi.org/10.1016/j.pedneo.2021.11.013.

[13] Terry K. Koo, Y. Li Mae, A guideline of selecting and reporting intraclass correlation coefficients for reliability Research, Journal of Chiropractic Medicine 15 (2) (2016) 155–163, https://doi.org/10.1016/j.jcm.2016.02.012.

[14] R Core Team, R: A Language and Environment for Statistical Computing, 2017. Manual. Vienna, Austria, https://www.R-project.org/.
[15] Hadley Wickham, Ggplot2: Elegant Graphics for Data Analysis, Springer-Verlag, New York, 2009. http://ggplot2.org.
[16] Erkan Sari, Sebahattin Sarı, Veysel Akgün, Emrah Özcan, Selami İnce, Oğuzhan Babacan, Mehmet Saldır, et al., Measures of ventricles and Evans' index: from neonate to adolescent, Pediatr. Neurosurg. 50 (1) (January 22, 2015) 12–17, https://doi.org/10.1159/000370033.
[17] Theresa Kagermeier, Stefan Hauser, Kseniia Sarieva, Lucia Laugwitz, Samuel Groeschel, Wibke G. Janzarik, Zeynep Yentür, et al., Human organoid model of pontocerebellar hypoplasia 2a recapitulates brain region-specific size differences, Disease Models & Mechanisms 17 (7) (July 1, 2024), https://doi.org/10.1242/dmm.050740 dmm050740.
[18] Peter L. Strick, Richard P. Dum, Julie A. Fiez, Cerebellum and nonmotor function, Annu. Rev. Neurosci. 32 (2009) 413–434, https://doi.org/10.1146/annurev.neuro.31.060407.125606.
[19] Leonard F. Koziol, Deborah Budding, Nancy Andreasen, Stefano D'Arrigo, Sara Bulgheroni, Hiroshi Imamizu, Masao Ito, et al., Consensus paper: the cerebellum's role in movement and cognition, Cerebellum 13 (1) (February 2014) 151–177, https://doi.org/10.1007/s12311-013-0511-x.
[20] Detlef H. Heck, Mia B. Fox, Brittany Correia Chapman, Samuel S. McAfee, Yu Liu, Cerebellar control of thalamocortical circuits for cognitive function: a review of pathways and a proposed mechanism, Front. Syst. Neurosci. 17 (March 30) (2023) 1126508, https://doi.org/10.3389/fnsys.2023.1126508.