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ORIGINAL ARTICLE

Expanding the natural history of CASK-related disorders to the prenatal period

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Abstract

Aim: To assess whether microcephaly with pontine and cerebellar hypoplasia (MICPCH) could manifest in the prenatal period in patients with calcium/calmodulin-dependent serine protein kinase (CASK) gene disorders.

Method: In this international multicentre retrospective study, we contacted a CASK parents' social media group and colleagues with expertise in cerebellar malformations and asked them to supply clinical and imaging information. Centiles and standard deviations (SD) were calculated according to age by nomograms.

Results: The study consisted of 49 patients (44 females and 5 males). Information regarding prenatal head circumference was available in 19 patients; 11 out of 19 had a fetal head circumference below –2SD (range –4.1SD to –2.02SD, mean gestational age at diagnosis 20 weeks). Progressive prenatal deceleration of head circumference growth rate was observed in 15 out of 19. At birth, 20 out of 42 had a head circumference below –2SD. A total of 6 out of 15 fetuses had a TCD z-score below –2 (range –5.88 to –2.02).

Interpretation: This study expands the natural history of CASK-related disorders to the prenatal period, showing evidence of progressive deceleration of head circumference growth rate, head circumference below –2SD, or small TCD. Most cases will not be diagnosed according to current recommendations for fetal central nervous system routine assessment. Consecutive measurements and genetic studies are advised in the presence of progressive deceleration of head circumference growth rates or small TCD.

Abbreviations: CASK, calcium/calmodulin-dependent serine protein kinase; MICPCH, microcephaly with pontine and cerebellar hypoplasia; PCH, pontocerebellar hypoplasia; TCD, transcerebellar diameter.

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Calcium/calmodulin-dependent serine protein kinase (CASK) is an essential protein in the presynaptic compartment, belonging to the membrane-associated guanylate kinases family of proteins, widely expressed in the brain.[1] Pathogenic variants are associated with two main phenotypes: loss of function variants present with microcephaly with pontine and cerebellar hypoplasia (MICPCH; OMIM #300749), while hypomorphic variants present with X-linked intellectual disability with or without nystagmus (OMIM #309590).[2,3] MICPCH is usually reported in females, and presents with progressive microcephaly, intellectual disability, seizures, ophthalmological anomalies, and sensorineural hearing loss.[2-5] Language is absent in most.[4] Severe pontine and cerebellar hypoplasia is depicted by magnetic resonance imaging (MRI). Microcephaly (occipitofrontal circumference –2.7SD to –9SD), usually develops within the first months of life. However, a third of the female and half of the male patients already demonstrate microcephaly at birth (occipitofrontal circumference below –2SD).[4] The rest are born with a head circumference within the normal to low-normal range.[4]

CASK gene-related MICPCH results mainly from de novo pathogenic variants, but copy number alterations, intragenic nonsense deletions, and exon-intron junction mutations have all been described.[2,3,6] The genetic diagnosis is usually made postnatally in individuals with a consistent clinical and imaging presentation.

We anticipated that MICPCH could already manifest during pregnancy, after the recent diagnosis of a *CASK* gene deletion, in a fetus with a small transcerebellar diameter (TCD) in the second trimester, and a retrospective observation of deceleration of head circumference growth rate at the end of pregnancy in two additional patients with CASK variants. To examine our theory, we contacted a CASK parents' social media group and colleagues with expertise in cerebellar malformations and asked them to supply clinical information, as well as prenatal and postnatal ultrasound and MRI.

What this paper adds

- Progressive deceleration of fetal head circumference growth rate can be observed.
- A small transcerebellar diameter is an additional important manifestation.
- Most cases will not be diagnosed according to current recommendations for fetal central nervous system routine assessment.
- Consecutive measurements are advised when measurements are within the low range of norm.

METHOD

This retrospective, multicentre study is part of the CASK International Consortium, a large international project on the prenatal diagnosis of CASK, which includes patients from eight centres in six countries (Israel, Italy, Switzerland, Canada, France, and Serbia).

We reviewed our patients' medical records (patients 1–3, Tables S1 and S2) including prenatal surveillance, prenatal ultrasound and MRI scans, and postnatal medical follow-up and imaging. We contacted a CASK parents group on social media. We asked the parents to fill in an online survey (Appendix S1) and to supply prenatal and postnatal ultrasound, MRI/reports, and medical and genetic records. We also contacted physicians from the pontocerebellar hypoplasia (PCH) consortium (an international multicentre project) and asked them to supply the same data.[6] Patients with CASK-related MICPCH, with confirmed genetic diagnosis and available head circumference measurements either prenatally or at birth, were included in the study.

The study was approved by the Edith Wolfson Medical Center institutional review board (WOMC-0288–20). The data were collected between May and October 2021. Written informed consent was obtained from all parents who filled out the survey. The combination of information including genetic variant, child's age, sex, and gestational age at birth allowed us to determine that there were no duplicate entries. The survey was comprised of open questions as well as multiple choice questions and checkboxes. Medical terminology amongst non-professional terms were used where applicable. Recruitment of study participants was done by publishing an online post in the CASK social media group with a link to the online survey. Caregivers of children with a medically confirmed diagnosis of a CASK pathogenic variant were invited to complete the survey. Further questions were answered in the original post, via private message or by email according to the caregivers' preferences. Centiles and standard deviations (SD) were calculated according to age by nomograms. Estimated fetal weight, head circumference, and biparietal diameter centiles and SDs were calculated using Hadlock et al.'s and Chervenak et al.'s reference ranges.[7,8,11] TCD z-scores were calculated according to Hill et al.'s reference range.[9] Newborn infants' head circumference and weight centiles and SD were calculated using Fenton's et al. reference ranges.[10] A small head circumference was defined as head circumference below –2SD both prenatally and postnatally.

RESULTS

The study consisted of 49 patients: three patients from our fetal neurology clinic and rare disease centre; 19 from the CASK gene parent support group (the survey was sent to 675 participants, 24 replied, three patients were excluded because of a lack of head circumference measurements); information regarding 26 patients was received from physicians associated with the PCH consortium (19 were contacted and 11 sent information). Two patients were excluded because of a CASK-related disorder that is not MICPCH. There were 44 females and five males.

The CASK variants, and prenatal and clinical information are detailed in Tables S1 and S2.

Fetal head circumference

Information regarding prenatal head circumference was available in 19 out of 49 patients. According to Hadlock et al.'s reference ranges,[8] 11 out of 19 patients had a fetal head circumference below −2SD (range −2.02SD to −4.1SD); mean age at diagnosis was 20 weeks' gestation (range 15–33 weeks gestational age). According to Chervenak et al.'s reference ranges, 6 out of 19 had a fetal head circumference below −2SD (range −2.01SD to −2.6SD).[11,12]

In 7 out of 19 fetuses, there were head circumference measurements from the second trimester only, in 4 out of 19 there were measurements from the third trimester only, and in 8 out of 19 there were measurements from both.

Seven fetuses lacked information regarding head circumference at birth, two were born with a normal head circumference (31 cm at 35 weeks' gestation), and eight were born with microcephaly (one of which had a head circumference within normal limits at 31 weeks' gestation).

A progressive prenatal deceleration of head circumference growth rate was observed in 15 out of 19: nine with measurements from both second and third trimester, one patient with measurements from the second trimester only, and the rest with measurements from the third trimester only. A deceleration starting in the second trimester was observed in all 10 fetuses with second trimester information. In three fetuses who only had measurements from the third trimester, a progressive deceleration was noted, but the exact gestational age at which it commenced remains unknown (Figure 1). The remaining 4 out of 19 fetuses (patients 3, 11, 39, 40) only had one measurement during pregnancy; therefore, it is unknown whether a deceleration of head circumference growth occurred.

Head circumference at birth

Information regarding head circumference at birth was available in 42 out of 49 patients, of which 20 out of 42 patients had a head circumference below −2SD (range −3.3SD to −2.02SD, mean −2.5SD), and the rest had a head circumference > −2SD at birth (range −1.54SD to 1SD, mean −0.61SD).

Fetal transcerebellar diameter

Fifteen fetuses had information regarding prenatal measurements of the TCD. The TCD was measured during 20 to 36 weeks' gestation. All fetuses except three had a single measurement. A total of 6 out of 15 fetuses had a TCD z-score below −2 (range −2 to −5.88), according to Hill et al.'s reference range.[9] The remaining 10 fetuses had a TCD ranging from −1.5SD to −1.75SD.

Prenatal MRI

Fetal MRIs were only obtained in two patients at 24 weeks' and 33 weeks' gestation. The causes of referral were central nervous system anomalies detected by ultrasound: agenesis of the corpus callosum (patient 10) and Chiari II malformation with myeloschisis (patient 14).

There was only one patient that was diagnosed in utero: patient 3, from our fetal neurology clinic. Cerebellar hypoplasia was diagnosed by ultrasound at 25 weeks, because of a TCD below −2SD (Figure 2). The mother underwent amniocentesis. Chromosomal microarray analysis revealed

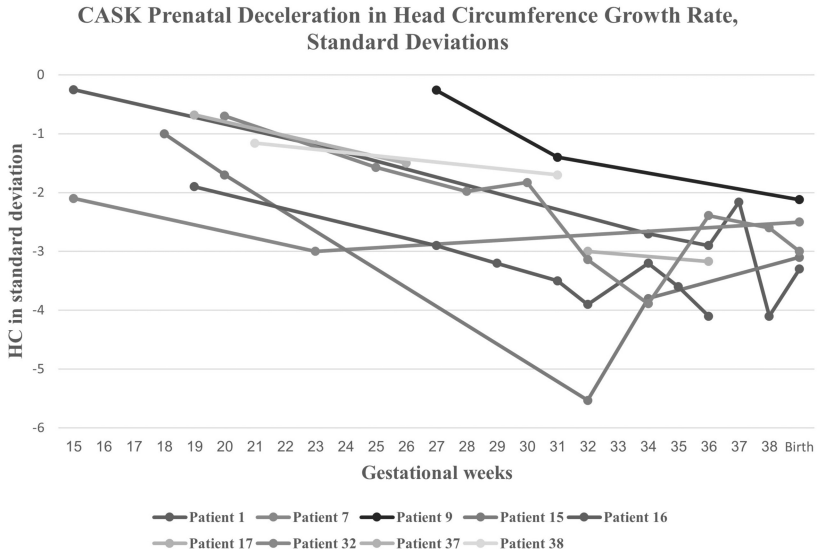

FIGURE 1 Prenatal deceleration of head growth in patients with calcium/calmodulin-dependent serine protein kinase-related disorders. HC, head circumference.

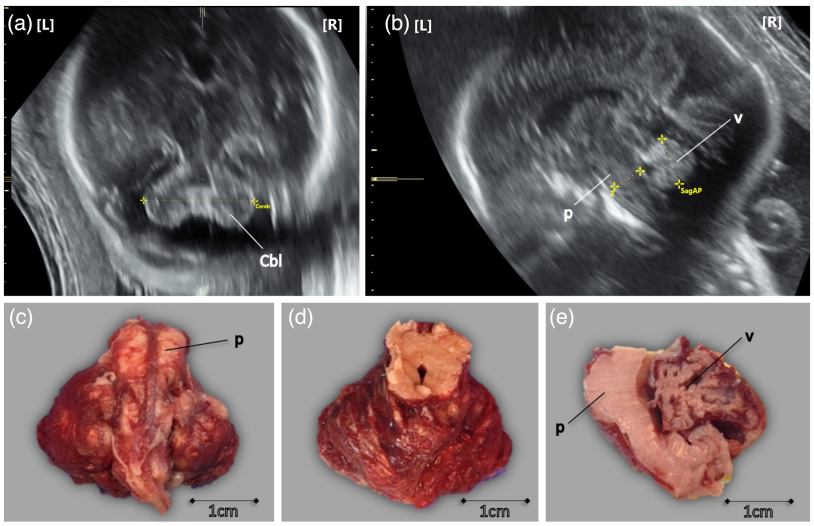

FIGURE 2 Sonograms and autopsy photographs of the cerebellum and brainstem of a fetus with *CASK* gene deletion (patient 3). (a) Axial transcerebellar sonogram at 29 weeks 6 days. Note a normal cerebellar morphology (Cbl) and a small for gestational age transcerebellar diameter (−3.1SD). (b) Midsagittal fetal head sonogram oriented to the posterior fossa at 29 weeks 6 days. Note normally shaped vermis and fastigium. The pons and vermis are within the lower limits of the normal range. Both sonograms were obtained from 3D multiplanar reformatting. (c,d,e) Anterior, posterior, and medially dissected autopsy images, correspondingly. Note the symmetric yet smaller than usual cerebellum, and a small and flattened pons (p, pons; v, vermis).

an Xp11 deletion including the *CASK* gene. After parental counselling regarding MICPCH, the parents elected to terminate the pregnancy at 30 weeks' gestation.

Postmortem analysis

The macroscopic evaluation revealed a symmetric yet smaller than usual cerebellum, with slightly wider than normal cisterna magna, and a small and flattened pons (Figure 2).

Genetic diagnoses

All patients carried variants in the *CASK* gene; large deletions (including exons deletions) were identified in 13 patients, nonsense variants (including splice variants) were identified in 31 patients, and five missense variants (including one single amino acid deletion) were identified in this study.

Genotype-phenotype correlation

Microcephaly, prenatal or at birth, presented in 24 out of 49 patients in this cohort: 6 out of 13 patients with microcephaly carried large deletions in the *CASK* gene, 16 out of 31 carried nonsense variants (including splice variants), and 2 out of 5 had missense variants.

Additional genetic findings

Three patients had additional genetic findings: patient 1 carried a duplication in 1q42.2 size 559 KB including three genes with unknown significance. Patient 14, who also had a myelomeningocele, carried a c.577 C>G (p.P193A) likely pathogenic variant in *ADAR* gene transmitted from their healthy mother. *ADAR* variants are known to cause Aicardi–Goutières syndrome;[13,14] however, the patient did not have any symptoms typical for this syndrome. Myelomeningocele has not been found to be related to *CASK* or *ADAR* variants.

DISCUSSION

The PCH encompass a group of neurodegenerative disorders that manifest radiologically and pathologically as hypoplasia/atrophy of the cerebellum and pons associated with microcephaly.[6,15] Since the original description of PCH by Barth in 1993,[15] the clinical phenotype has been considerably extended, and the current classification of PCH comprises 16 subtypes (PCH1–16), most progressive.[16,17]

Najm et al. first described CASK-related MICPCH in 2008 as congenital and postnatal microcephaly with disproportionate brainstem and cerebellar hypoplasia, and severe intellectual disability.[18]

Moog et al. reported the clinical presentation of 25 patients with CASK pathogenic variants.[5] The occipitofrontal circumference at birth was in the normal or low-normal range in 16 affected females, and below −2SD in nine.[5]

Van Dijk et al.[19] have recently published the postnatal brain growth patterns in a cohort of 66 patients with PCH, including six patients with *CASK* gene variants. The head circumference at birth is not mentioned, but the authors concluded that the cerebellum was severely hypoplastic at birth in all patients with CASK-related disorders and showed very limited postnatal growth.

Knockout mouse models corroborate evidence for a postnatal neurodegenerative process as compared to a primary developmental defect with respect to the severe and stereotypical pontocerebellar changes in complete CASK loss of function.[20] Our findings support the notion that CASK-related disorders are, in some cases, progressive disorders with prenatal onset. The timing of pontocerebellar growth restriction likely depends on the degree of the CASK loss of function and lies within a continuum.

In one case report, a fetus with a prenatal diagnosis of intrauterine growth restriction and 'extremely small cerebellum and mega cisterna magna' was postnatally diagnosed with a loss on Xp11.4, an inactivating mutation involving exon 5 of the *CASK* gene.[21] To the best of our knowledge, apart from the case report mentioned above, there are no reports in the literature on the prenatal diagnosis of CASK. In our study, 11 out of 19 fetuses had a prenatal head circumference below −2SD (range −2.02SD to −4.1SD, mean −2.9SD) according to Hadlock et al.'s reference ranges, and 6 out of 19 had a fetal head circumference below −2SD (range −2.01SD to −2.6SD) according to Chervenak et al.'s reference ranges[7,10,11] (Tables S1 and S2); however, our case was the only one diagnosed in utero. A progressive deceleration of head circumference growth during either the second or third trimesters was observed in 33 fetuses (Figure 2). At birth, 20 out of 42 patients (48%) had a head circumference below −2SD (range −3.3SD to −2.02SD), higher than the 36% previously reported by Moog et al.[5]

The diagnosis of fetal microcephaly is challenging. As previously discussed in a study by Leibovitz et al., the yield of the commonly used growth charts for prenatal diagnosis of microcephaly is low, and there is significant discrepancy between them.[22] Nevertheless, fetal deceleration of head circumference growth rate regardless of the reference range should be considered a 'red flag' and warrants further evaluation.[23]

The scarcity of prenatal diagnosis of microcephaly in patients with CASK variants is difficult to understand even though around 50% are born with a head circumference below −2SD but can be due to development of microcephaly after the anatomic scan at 22 weeks and lack of measurements in the third trimester. Therefore, most cases will not be diagnosed according to current recommendations for the routine fetal central nervous system assessment. Furthermore, the definition of fetal microcephaly is considered a head circumference ≤ −3SD, while the definition of postnatal microcephaly is below −2SD; there is no universal policy to recommend a deeper evaluation of the brain between −2SD and −3SD, therefore many fetuses are not diagnosed in utero (only postnatally).

In our study, 6 out of 15 fetuses had a TCD below −2SD according to Hill et al.'s reference range.[9] However, our patient was the only one who was diagnosed as having cerebellar hypoplasia in utero. This again is difficult to explain but may be due to only a single measurement during pregnancy, with no follow-up of small TCD measurements, the use of different reference ranges, and low awareness of the importance of TCD measurements. Unfortunately, we do not have information regarding TCD at birth because imaging studies were not obtained.

Based on our results, we emphasize the importance of consecutive head circumference and TCD measurements throughout gestation, especially in the third trimester. Nevertheless, the prenatal ultrasound will only flag a subset of fetuses affected by a CASK-related disorder. Fetuses with head circumference or TCD measurements below 2SD or with a deceleration of their growth, mainly if disproportionate to their estimated fetal weight growth rate, should have a genetic evaluation.[24,25]

The genetic assessment should not be limited to CASK since there is a broad differential diagnosis for microcephaly with or without cerebellar hypoplasia, including chromosomal abnormalities, single gene disorders, and inborn error of metabolism.[24-28] Therefore, we recommend next generation sequencing approaches as part of the prenatal evaluation in suspected cases.

Interestingly, our study demonstrated that all variant categories were observed almost equally in fetuses with or without a prenatal presentation, indicating that there is no clear phenotype–genotype correlation.

Unexpectedly, two patients presented with central nervous system abnormalities on MRI that are not known to be associated with the CASK phenotype: complete agenesis of the corpus callosum with normal appearance of the cerebellum and brain stem (patient 10, 33 weeks' gestation), and Chiari II malformation with hindbrain herniation, spina bifida, and lumbosacral myeloschisis (patient 14, 24 weeks' gestation). Moog et al. have also expanded the clinical phenotype of CASK variants and described additional congenital anomalies such as fusion of kidneys, mitral valve incompetence, pectus excavatum, and hypoplastic toenails. They stated that these malformations were only seen in a minority of patients and no specific anomaly reoccurred.[6] Therefore, it is unclear whether these malformations and the ones described in our study were directly related to the CASK variant.

The main limitation of our study is the small sample size because of a low response rate (24/675) of parents from the CASK social media group and lack of available prenatal measurements from the physicians associated with the PCH consortium. The lack of sufficient prenatal data can also be attributed to the age of some of the patients, born when prenatal testing, such as prenatal MRI, was less frequently performed.

Another limitation is the retrospective nature of the study, which results in variability in the data provided by the caregivers, such as the timing of the head circumference, biparietal diameter, and TCD measurement acquisition. However, all measurements were converted into standard deviations and centiles according to gestational age using acceptable nomograms as detailed in the 'Method', allowing us to compare them.[7,8,29,30] Furthermore, several caregivers provided consecutive measurements, which allowed us to evaluate the fetus's growth trajectories, rather than relying on a single measurement. Nevertheless, further

prospective study is needed to better define the feasibility and predictive value of consecutive prenatal head circumference measurements.

The use of a questionnaire was valuable for certain information (e.g. gestational week at birth, patient's sex); however, for assessing the patient's neurodevelopmental outcome (e.g. verbal and motor skills, presence of seizures and autistic features, etc.), the assembled data varied in quality, and further clarification could not be obtained because of the anonymous nature of the data acquisition. This information was not of sufficient quality to be included in this study. In a future study, a better way to obtain higher quality clinical information might be in the form of a personal interview or reports from an attending physician.

Lastly, a selection bias might influence the prevalence of the patients with microcephaly in our cohort, which was observed in half of our population, whereas the known prevalence is only a third of female and half of male patients.[4] Although we asked all caregivers of patients with CASK-related disorders and colleagues to share information, regardless of whether they had abnormal head circumference (prenatal or at birth), the purpose of the study was overt to all participants. Therefore, there may have been a greater willingness to participate on the part of parents who thought their children had a small head circumference at birth.

Conclusion

This study expands the natural history of CASK-related disorders to the prenatal period, showing evidence of a progressive deceleration of fetal head circumference growth rate, a fetal head circumference below –2SD, and a small TCD. Consecutive measurements, especially in the third trimester, are important to detect deceleration of fetal head circumference and TCD growth rates, even in fetuses with measurement within the normal ranges. Closer monitoring is especially important when the measurements are within the low range of the norm. Amniocentesis is warranted for genetic studies, including whole exome sequencing (permitting diagnosis of other causes of fetal microcephaly and cerebellar hypoplasia) and chromosomal microarray analysis (permitting diagnosis of *CASK* gene deletions), to allow adequate counselling and enabling informed decision-making by parents.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION

The following additional material may be found online:
Appendix S1: Online survey
Table S1: CASK pathogenic variants, prenatal information
Table S2: Postnatal and clinical information

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