Original Article

Journal of Child Neurology
1-7

DOI: 10.1177/0883073820960314
journals.sagepub.com/home/jcn
SAGE

Chudley-McCullough Syndrome: A Recognizable Clinical Entity Characterized by Deafness and Typical Brain Malformations

Aglaë Blauen, MD[1], Chloe A. Stutterd, MD[2,3,4], Katrien Stouffs, MSc, PhD[5,6], Dana Dumitriu, MD[7], Naima Deggouj, MD[8], Paul J. Lockhart, PhD[3,4], Richard J. Leventer, MD, PhD[2,3,4], Marie-Cécile Nassogne, MD, PhD[1], and Anna C. Jansen, MD, PhD[6,9]

Abstract

Chudley-McCullough syndrome, a rare autosomal recessive disorder due to pathogenic variants in the *GPSM2* (G-protein signaling modulator 2) gene, is characterized by early-onset sensorineural deafness and a typical combination of brain malformations, including ventriculomegaly, (partial) agenesis of the corpus callosum, cerebellar dysplasia, arachnoid cysts, frontal subcortical heterotopia, and midline polymicrogyria. When hearing loss is managed early, most patients have minor or no impairment of motor and cognitive development, despite the presence of brain malformations. We report 2 cases of Chudley-McCullough syndrome, one presenting with congenital deafness and normal development except for speech delay and one presenting prenatally with ventriculomegaly and an atypical postnatal course characterized by epileptic spasms, deafness, and moderate intellectual disability. These highlight the challenges faced by clinicians when predicting prognosis based on pre- or postnatal imaging of brain malformations. We have also reviewed the phenotype and genotype of previous published cases to better understand Chudley-McCullough syndrome.

Keywords

GPSM2, ventriculomegaly, corpus callosum dysgenesis, frontal dysplasia, polymicrogyria, cerebellar hypoplasia

Received May 28, 2020. Received revised August 4, 2020. Accepted for publication August 28, 2020.

Sensorineural hearing loss affects approximately 1/1000 children. Genetic causes account for 60%, with more than 40 causative genes identified. Sensorineural deafness is also a feature of approximately 300 syndromes, including the Chudley-McCullough syndrome (CMS).[1]

The differential diagnosis of deafness and (partial) agenesis of the corpus callosum includes pathogenic variants in *CDK 10*,[2] *SEC31A*[3] *and YARS*,[4] Mowat-Wilson syndrome,[5] arthrogryposis–renal dysfunction–cholestasis syndrome,[6] Donnai-Barrow syndrome,[7] Wolfram syndrome,[8] and congenital cytomegalovirus infection.

Chudley-McCullough syndrome was first described in 1997 by Chudley in a consanguineous Canadian-Mennonite dizygotic twin pair.[9] This syndrome is characterized by early-onset sensorineural deafness and a combination of developmental brain malformations including colpocephaly, partial agenesis of the corpus callosum, cerebellar dysplasia, arachnoid cysts, frontal subcortical heterotopia and frontal polymicrogyria which, when present together are almost pathognomonic for Chudley-McCullough syndrome.[10] It is crucial to be aware of this association, since the prognosis is generally good, despite these severe brain malformations. In 2012, Doherty et al[10] linked Chudley-McCullough syndrome to homozygous inactivating

[1] Pediatric Neurology Unit, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
[2] Department of Neurology, Royal Children's Hospital, Melbourne, Australia
[3] Murdoch Children's Research Institute, Melbourne, Australia
[4] Department of Pediatrics, University of Melbourne, Melbourne, Australia
[5] Center for Medical Genetics, UZ Brussel, Brussels, Belgium
[6] Neurogenetics Research Group, Reproduction—Genetics & Regenerative Medicine Research Cluster, Vrije Universiteit Brussel, Brussels, Belgium
[7] Pediatric Radiology Unit, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
[8] Department of Oto-Rhino-Laryngology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
[9] Pediatric Neurology Unit, Department of Pediatrics, UZ Brussel, Brussels, Belgium

Corresponding Author:
Aglaë Blauen, MD, Pediatric Neurology Unit, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, avenue Hippocrate 10, B-1200 Brussels, Belgium.
Email: aglae.blauen@student.uclouvain.be

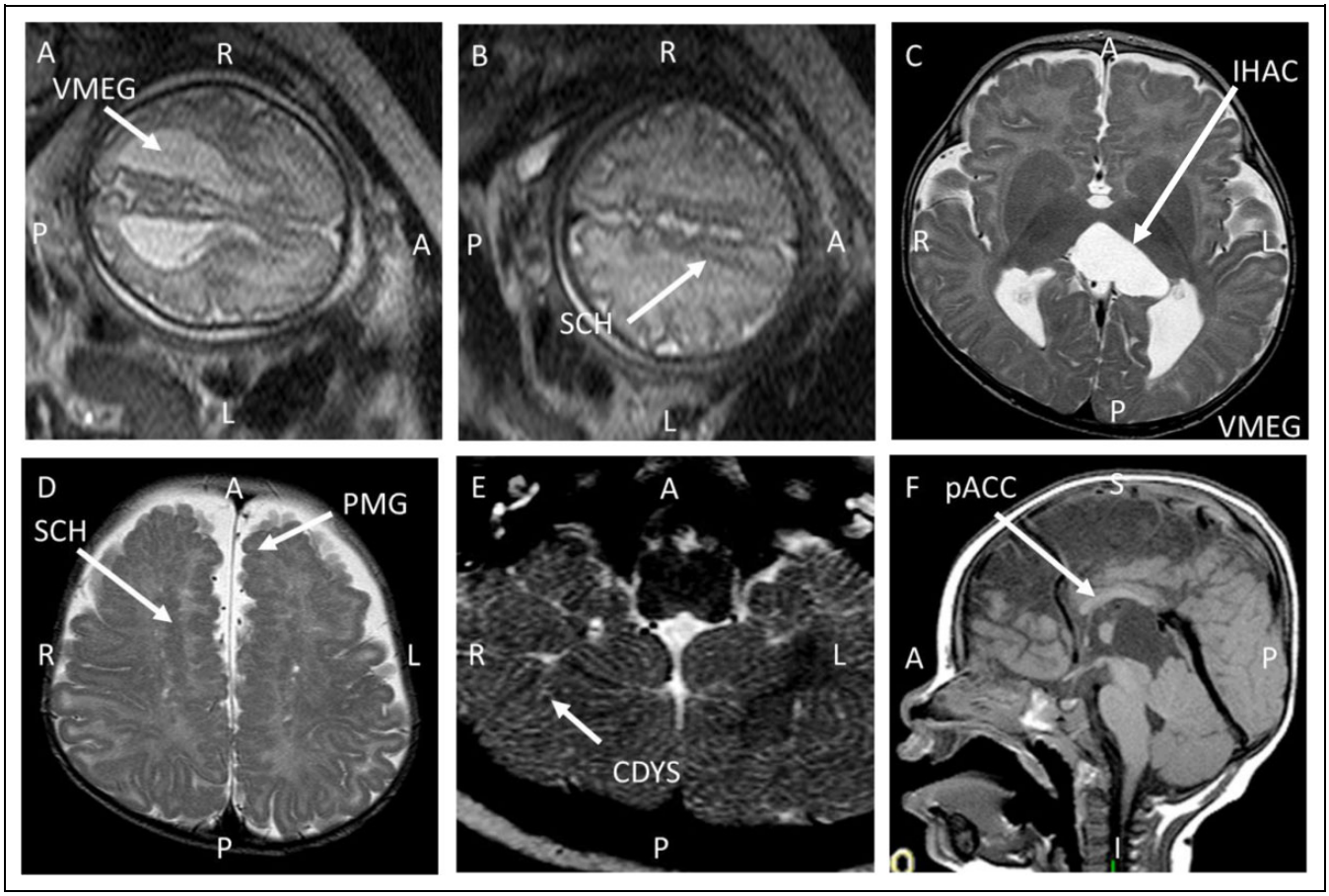

Figure 1. Patient 1 neuroimaging. Third-trimester prenatal axial T2-weighted magnetic resonance imaging (MRI) (A and B), showing ventriculomegaly (VMEG) and subcortical heterotopia (SCH). Postnatal brain MRI axial T2-weighted (C, D, and E) and sagittal T1-weighted (F) imaging performed at 5 months, showing an interhemispheric arachnoid cyst (IHAC), ventriculomegaly (VMEG), frontal polymicrogyria (PMG), bi-frontoparietal subcortical heterotopia (SCH), cerebellar dysgenesis (CDYS), and partial agenesis of the corpus callosum (PACC).

variants in the gene encoding G-protein signaling modulator 2 (GPSM2). This protein regulates actin cytoskeleton polymerization during stereocilia elongation, corpus callosum formation, and neuronal outgrowth.[11] So, GPSM2 plays a role in spindle pole orientation and in neuroblast division. *GPSM2* variants cause alterations in neuronal migration and corticomedullary differentiation, resulting in gray matter heterotopia, as well as cerebral and cerebellar hypoplasia. GPSM2 is abundant at the apical surfaces of hair cells and supporting cells of the inner ear during early embryogenesis. Pathogenic variants lead to alterations in cell polarity and function, resulting in sensorineural hearing loss.

Since 2012, 22 cases with 8 different variants in *GPSM2* have been reported. Here we report 2 individuals with Chudley-McCullough syndrome associated with bilateral sensorineural deafness and typical brain malformations but with variable clinical prognosis.

Patients and Methods

We report 2 cases of Chudley-McCullough syndrome with variable neurodevelopmental outcome.

Results

Patient one is a 14-year-old boy, the first child of a consanguineous union, his parents being first cousins and in good health. Prenatal ultrasonography at 22 weeks' gestation showed isolated colpocephaly. At 28 weeks, fetal magnetic resonance imaging (MRI) confirmed colpocephaly with occipital horns of 17 mm and 14.5 mm, respectively, considered as a moderate to severe ventriculomegaly, and a thin corpus callosum. To evaluate the progression of the ventriculomegaly, a second MRI was performed at 32 weeks' gestation, which confirmed a stable isolated colpocephaly (Figure 1). In retrospect, fetal MRI revealed bifrontal gray matter heterotopia (Figure 1). Karyotype analysis performed on amniotic fluid cells and screening for cytomegalovirus and toxoplasmosis were negative.

The infant was delivered at 36 weeks 3 days and did well in the newborn period. Birth weight was 3240 g (75th percentile), height 52 cm (97th percentile), and head circumference 35.8 cm (90th percentile). Clinical examination revealed mild axial hypotonia. Cerebral ultrasonography on postnatal day 1 confirmed colpocephaly and a short corpus callosum. At

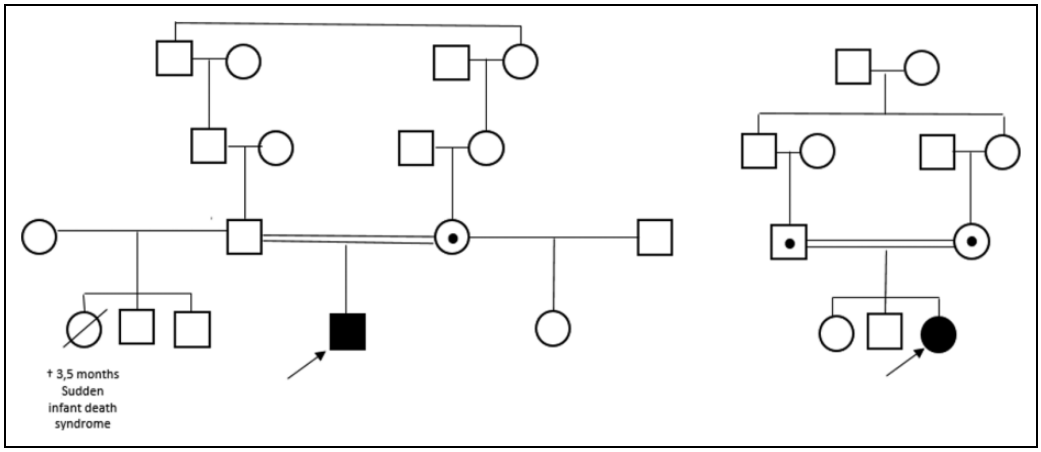

Figure 2. Pedigree of family 1 (left) and family 2 (right).

5 months, brain MRI showed ventriculomegaly, partial agenesis of the corpus callosum, frontal polymicrogyria, bilateral frontoparietal subcortical heterotopia, cerebellar dysplasia, and an interhemispheric arachnoid cyst (Figure 1).

At 6 months of age, neurologic development was appropriate for age but the child developed epileptic spasms, confirmed by electroencephalography (EEG) and treated with vigabatrin. Spasms were rapidly controlled and EEG normalized. Vigabatrin was discontinued at 19 months of age.

An audiologic assessment at age 17 months revealed profound bilateral sensorineural hearing loss on pure-tone audiometry. Behavioral reactions were evoked by speech presented at 80 dB on the left and 85 dB on the right side. Brainstem auditory-evoked potentials did not identify any reproducible response after stimulating right and left ears. Etiologic assessment using computed tomography scanning of the temporal bones, ear MRI, and genetic analysis of the gene encoding gap junction beta 2 (GJB2) excluded the most common causes of severe-to-profound nonsyndromic deafness. Conventional acoustic hearing aids were provided bilaterally at 17 months.

At age 18 months, global development delay was noticed, predominantly in language development. Because hearing aids were unsatisfactory, a right cochlear implant was inserted at 21 months and speech therapy was initiated. With the implant, the child progressed in language development, and his tonal audiometry improved, with reaction to voice present at 35 dB. At age 5 years, a contralateral cochlear implant was inserted. Tonal and speech audiometry were satisfactory with the 2 implants. The child received special education services. Because of persisting concerns about developmental functioning, intelligence quotient (IQ) testing using Wechsler Intelligence Scale for Children, Fourth Edition, (WISC-IV), was performed at age 13 years and showed moderate intellectual disability, with verbal comprehension index of 50 and perceptual reasoning index of 50 (0.25th percentile). At age 14 years, a new etiologic assessment by Mendeliome analysis of whole exome sequence data revealed a homozygous pathogenic variant *GPSM2*: NM_013296.4: c.742del; p.(Gly249Glufs*32), which confirmed the diagnosis of Chudley-McCullough syndrome. No other potentially pathogenic variants were detected. Parental analysis revealed that the mother was a heterozygous for the variant, whereas testing the child's father was not possible (Figure 2).

The second patient is a 7-year-old girl who presented at 2 years of age with congenital deafness and was referred to neurology following unexpected MRI findings during workup for cochlear implants. Brain MRI showed cerebellar dysplasia, partial agenesis of corpus callosum, ventriculomegaly, midline polymicrogyria, and a quadrigeminal arachnoid cyst (Figure 3). At age 5 years, development was normal, except for speech delay related to hearing loss. She has had cochlear implant insertion and cyst fenestration. At age 7 years, she attends a regular school with facilities for the hearing impaired. She has speech impairment secondary to sensorineural hearing loss and otherwise normal neurodevelopment. Formal evaluation of intellectual abilities was not performed. She has weekly speech therapy and communicates predominantly with sign language. A Haloplex gene panel including 287 genes that are known or candidate for brain malformation revealed a homozygous novel truncating variant in *GPSM2* (NM_013296.5 (GPSM2): c.1501delA; p.(Ser501Alafs*30)), inherited from consanguineous parents of Turkish origin (Figure 2). This confirmed the diagnosis of Chudley-McCullough syndrome.

Discussion

These cases highlight 3 important findings. First, the brain malformations associated with Chudley-McCullough syndrome are highly recognizable and might assist with confirming the diagnosis and with counseling patients and families. The findings on MRI include bilateral frontal subcortical heterotopia, midline polymicrogyria, (partial) agenesis of the corpus callosum, arachnoid cysts, ventriculomegaly or hydrocephalus, and striking cerebellar dysplasia in the absence of cerebellar signs on neurologic examination (Figures 1 and 3).

Second, the neurodevelopmental outcome associated with Chudley-McCullough syndrome is generally good, provided that

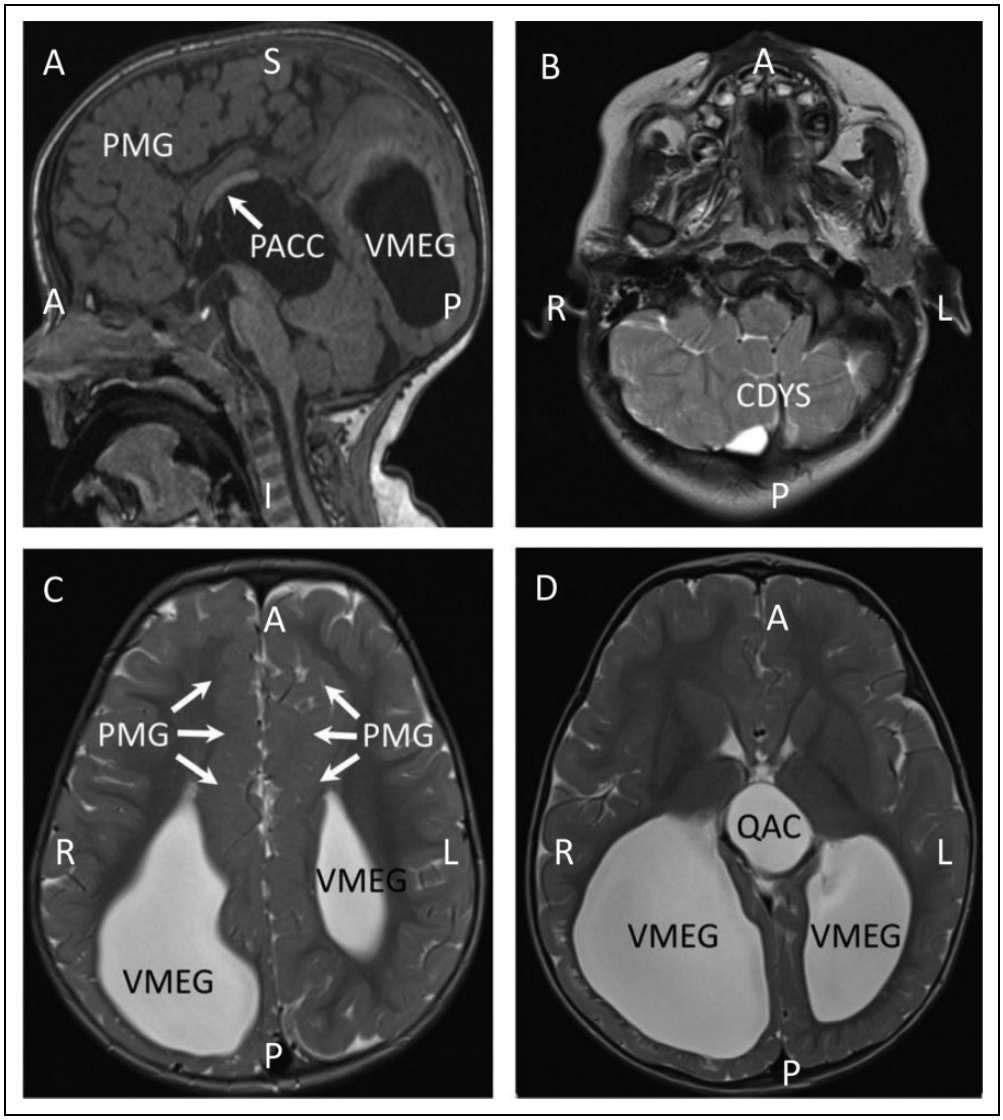

Figure 3. Patient 2 neuroimaging. (A) Midline sagittal T1-weighted magnetic resonance imaging (MRI) and (B, C and D) axial T2-weighted MRI showing extensive parasagittal polymicrogyria (PMG), partial agenesis of corpus callosum (PACC), ventriculomegaly (VMEG), quadrigeminal arachnoid cyst (QAC), and severe cerebellar dysgenesis (CDYS).

hearing loss is detected and managed at an early age (Table 1). This has important implications for prenatal counseling. When confronted with ventriculomegaly in combination with other brain malformations such as subcortical heterotopia or agenesis of the corpus callosum, prognosis is generally expected to be poor.[16] Chudley-McCullough syndrome is an exception to this rule, making the recognition of this syndrome on prenatal MRI even more relevant to assist with prenatal counseling. Fetal brain MRI findings in Chudley-McCullough syndrome have previously been reported in a single case by Chapman et al.[17] It was suggested that frontal cortical dysplasia, medial frontal heterotopia, or inferior cerebellar dysplasia should raise suspicion for Chudley-McCullough syndrome and prompt for confirmatory prenatal genetic testing in order to correctly counsel the family.[17] In patient 1, however, none of the brain malformations described in Chudley-McCullough syndrome were recognized on fetal MRI, and based on isolated, moderate, and stable ventriculomegaly, a favorable neurodevelopmental outcome was predicted. The difficulty in recognizing subtle brain malformations on fetal MRI may be accounted for by the well-known technical limits and interpretation difficulties of fetal MRI, which further complicates antenatal diagnosis and counseling.[17]

Third, patient 1 in this report highlights the fact that although all previously reported cases were associated with relatively good outcomes, epilepsy and moderate intellectual disability may occur in, respectively, 12% and 25%, further complicating counseling (Table 1). Review of published cases of genetically confirmed cases of Chudley-McCullough syndrome points to a gap in performing and/or reporting comprehensive neurodevelopmental evaluations in these individuals, including not only speech and language development but also formal evaluations of cognitive, motor, and social skills. These data will assist

Table 1. Clinical Cases Associated With GPSM2 Mutation: Neuroimaging Features and Neurodevelopment in Patientns With GPSM2-Related Chudley-McCullough Syndrome.

Authors	GPSM2 Mutation	VMG	CC agenesis	Arachnoid cyst	Cerebellar dysplasia	Frontal subcortical heterotopia	Frontal dysplasia	Deafness	Motor delay	Language delay	Cognitive impairment	Seizures
Walsh 2010[12]	c.379C>T	N	Y	Y	Y	Y	Y	**Y**	N	N	N	N
Yariz 2012[13]	c.1684C>T	N	Y	Y	N	Y	Y	**Y**	N	N	N	N
Yariz 2012[13]	c.1684C>T	N	Y	Y	Y	Y	Y	**Y**	N	N	N	N
Yariz 2012[13]	c.1684C>T	N	Y	Y	Y	Y	Y	**Y**	N	N	N	N
Doherty 2012[10]	c.1473delG	Y	Y	Y	?	Y	Y	**Y**	Mild	Mild	N	N
Doherty 2012[10]	c.1473delG	Y	Y	?	Y	Y	Y	**Y**	N	N	N	N
Doherty 2012[10]	c.1473delG	Y	Y	N	Y	Y	Y	**Y**	N	Y	Mild	N
Doherty 2012[10]	c.1473delG	Y	Y	Y	Y	Y	Y	**Y**	Y	Y	Mild to moderate	Y
Doherty 2012[10]	c.1473delG	Y	Y	Y	N	Y	Y	**Y**	Mild	Mild	Mild	N
Doherty 2012[10]	c.742delC	Y	Y	?	?	?	?	**Y**	N	N	N	N
Doherty 2012[10]	c.742delC	Y	Y	?	?	?	?	**Y**	N	Mild, resolved	N	N
Doherty 2012[10]	c.742delC	Y	Y	Y	Y	Y	Y	**Y**	Mild	N	N	N
Doherty 2012[10]	c.742delC + C.1661C>A	Y	Y	Y	Y	Y	Y	**Y**	N	N	Mild, resolved	N
Doherty 2012[10]	c.742delC + C.1661C>A	Y	Y	Y	Y	Y	Y	**Y**	Mild	Mild, resolved	Mild, resolved	Y
Doherty 2012[10]	c.1062+1G>T	Y	Y	Y	Y	Y	Y	**Y**	Mild	N	N	N
Doherty 2012[10]	c.1062+1G>T	Y	Y	Y	Y	Y	Y	**Y**	Mild	N	N	N
Almomani 2012[14]	c.1473delG	Y	Y	Y	N	N	N	**Y**	N	N	N	N
Almomani 2012[14]	c.1473delG	Y	Y	Y	N	N	N	**Y**	N	N	N	N
Almomani 2012[14]	c.1473delG	Y	Y	Y	Y	Y	Y	**Y**	N	Resolved	N	N
Koenigstein 2016[1]	c.1093C>T	Y	Y	Y	Y	N	Y	**Y**	N	N	N	N
Koenigstein 2016[1]	c.1093C>T	Y	Y	Y	Y	N	Y	**Y**	N	N	N	N
Forli 2019[15]	c.1471delG	Y	Y	Y	Y	N	Y	**Y**	N	N	N	N
Our case (1), 2020	c.742del	Y	Y	Y	Y	Y	Y	**Y**	Y	Y	Moderate	Y
Our case (2), 2020	c.1501delA	Y	Y	Y	Y	Y	Y	**Y**	N	Y	N	N
Percentages		83	100	83	71	71	83	**100**	33	37	25	12

Abbreviations: CC, corpus callosum, N, no; VMG, ventriculomegaly; Y, yes.

clinicians with counseling Chudley-McCullough syndrome families in the future.

Literature review further highlights that severe-to-profound congenital or early-onset deafness in combination with (partial) agenesis of the corpus callosum are the core features of Chudley-McCullough syndrome, since they are present in all previous reports and our patients (Table 1).

Finally, pathogenic variants in *GPSM2* seem to be highly specific of Chudley-McCullough syndrome and have not been reported in association with any other brain malformation or neurodevelopmental disease.

Conclusion

Our report highlights the presence of a recognizable pattern of brain malformations associated with Chudley-McCullough syndrome on MRI. The pattern is more challenging to recognize on fetal MRI, but the presence of frontal cortical dysplasia, medial frontal heterotopia, or inferior cerebellar dysplasia should raise suspicion for Chudley-McCullough syndrome. Neurodevelopmental outcome, although not always reported in detail, is favorable in general, as illustrated by patient 2. However, caution should be taken because moderate intellectual disability and epilepsy can be part of Chudley-McCullough syndrome, as illustrated by patient 1. Apart from the brain malformations, moderate to profound sensorineural hearing loss is the other hallmark of Chudley-McCullough syndrome. All children with hearing loss of unknown etiology should therefore be assessed with brain MRI and be tested for pathogenic variants in *GSPM2* in the presence of suggestive findings. Parents must be informed that for Chudley-McCullough syndrome, the recurrence risk is 25% for each consecutive pregnancy, and that Chudley-McCullough syndrome patients must be monitored for the development of hydrocephalus because this may require shunt placement.

Author Contributions

AB wrote the manuscript with support from M-CN and ACJ. M-CN, ACJ, CAS, KS, DD, ND, PJL and RJL. provided data. All authors reviewed the final manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: PJL is supported by the Vincent Chiodo Foundation. ACJ is supported by a Senior Clinical Investigator Fellowship from the Research Fund Flandres (FWO). CAS is supported by the Campbell Edwards Trust and the Royal Children's Hospital/Murdoch Children's Research Institute Flora Suttie Neurogenetics Fellowship made possible by the Suttie Family, the Thyne-Reid Foundation, and the Macquarie Foundation. RJL is supported by a Melbourne Children's clinician scientist fellowship.

Ethical Approval

The parents of both patients provided their consent for scientific publication.

ORCID iD

Aglaë Blauen, MD https://orcid.org/0000-0003-3351-3489

References

1. Koenigstein K, Gramsch C, Kolodziej M, et al. Chudley-McCullough Syndrome: variable clinical picture in twins with a novel *GPSM2* mutation. *Neuropediatrics*. 2016;47:197-201.
2. Guen VJ, Edvardson S, Fraenkel ND, et al. A homozygous deleterious CDK10 mutation in a patient with agenesis of corpus callosum, retinopathy, and deafness. *Am J Med Genet*. 2018; 176:92-98.
3. Halperin D, Kadir R, Perez Y, et al. SEC31A mutation affects ER homeostasis, causing a neurological syndrome. *J Med Genet*. 2019;56:139-148.
4. Tracewska-Siemiatkowska A, Haer-Wigman L, Bosch DGM, et al. An expanded multi-organ disease phenotype associated with mutations in *YARS*. *Genes*. 2017;8(12):381.
5. Abdalla EM, Zayed LH. Mowat-Wilson syndrome: deafness in the first Egyptian case who was conceived by intracytoplasmic sperm injection. *J Child Neurol*. 2014;29:168-170.
6. Bull LN, Mahmoodi V, Baker AJ, et al. VPS33B mutation with ichthyosis, cholestasis, and renal dysfunction but without arthrogryposis: incomplete ARC syndrome phenotype. *J Pediatr*. 2006; 148:269-271.
7. Khalifa O, Al-Sahlawi Z, Imtiaz F, et al. Variable expression pattern in Donnai-Barrow syndrome: report of two novel LRP2 mutations and review of the literature. *Eur J Med Genet*. 2015;58: 293-299.
8. Kinsley BT, Firth RG. The Wolfram syndrome: a primary neurodegenerative disorder with lethal potential. *Ir Med J*. 1992;85: 34-36.
9. Chudley AE, McCullough C, McCullough DW. Bilateral sensorineural deafness and hydrocephalus due to foramen of Monro obstruction in sibs: a newly described autosomal recessive disorder. *Am J Med Genet*. 1997;68(3):350-356.
10. Doherty D, Chudley AE, Coghlan G, et al. *GPSM2* mutations cause the brain malformations and hearing loss in Chudley-McCullough syndrome. *Am J Med Genet*. 2012;90:1088-1093.
11. Mauriac SA, Hien YE, Bird JE, et al. Defective Gpsm2/Gαi3 signalling disrupts stereocilia development and growth cone actin dynamics in Chudley-McCullough syndrome. *Nat Commun*. 2017;8:14907.
12. Walsh T, Shahin H, Miller TE, Lee MK, Thornton AM. Whole exome sequencing and homozygosity mapping identify mutation in the cell polarity protein GPSM2 as the cause of nonsyndromic hearing loss DFNB82. *Am J Med Genet*. 2010;87:90-94.
13. Yariz KO, Walsh T, Akay H, et al. A truncating mutation in GPSM2 is associated with recessive non-syndromic hearing loss. *Clin Genet*. 2012;81:289-293.

14. Almomani R, Sun Y, Aten E, et al. GPSM2 and Chudley-McCullough syndrome: a Dutch founder variant brought to North America. *Am J Med Genet*. 2012;161A:973-976.
15. Forli F, Fiacchini G, Bruschini L, Caniglia M, Berrettini S. Cochlear implant in a subject affected by the Chudley-McCullough syndrome. *Cochlear Implants Int*. 2019;20:217-221.
16. Volpe JJ, Inder TE, Darras BT, et al. Congenital hydrocephalus. In: Volpe JJ, ed. *Volpe's Neurology of the Newborn*. 6th ed, Chapter 3. Philadelphia, PA: Elsevier; 2018.
17. Chapman T, Perez FA, Ishak GE, Doherty D. Prenatal diagnosis of Chudley-McCullough syndrome. *Am J Med Genet*. 2016;170A: 2426-2430.