Colpocephaly in Chudley-McCullough Syndrome

Adriaan RE. Potgieser1*, Erica H. Gerkes2, and Eelco W. Hoving1
1Department of Neurosurgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.
2Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

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*Corresponding author: Adriaan RE. Potgieser, Department of Neurosurgery, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30.001, 9700 RB Groningen, The Netherlands, Tel: +31-503-612-837; Fax: +31-503-611-715; E-mail: a.r.e.potgieser@umcg.nl.

Abstract
Background: Chudley-McCullough syndrome is a rare autosomal recessive disorder characterized by congenital bilateral sensorineural hearing loss, partial corpus callosum agenesis, colpocephaly with a right-sided tendency and other brain abnormalities, such as an anorchid cyst.

Main findings: In this case report we present two adult sisters with asymmetrical enlarged ventricles who were treated surgically under the assumption of "hydrocephalus", yielding no clinical benefit. They were diagnosed subsequently with the Chudley-McCullough syndrome. The enlarged ventricles in this syndrome are secondary to a developmental malformation called colpocephaly, instead of a true hydrocephalus based on a cerebrospinal fluid circulation disturbance.

Conclusion: The ventriculomegaly in Chudley-McCullough syndrome is secondary to colpocephaly and not caused by a true hydrocephalus and thus we recommend conservative follow-up without cerebrospinal fluid diversion.

Keywords: Hydrocephalus; Chudley-McCullough syndrome; GPSM2; Colpocephaly

Case Report

We describe two sisters that came to our attention because one of the sisters was referred to our clinic. The parents reminded us that the other sister, also present during the visit, had a more or less comparable phenotype and was operated in our clinic more than ten years ago. It was the similarity between the two cases that prompted us to find a common denominator. This coincidence of the two sisters coming to our clinic together, during which we saw a remarkably similar colpocephaly, led to the delayed diagnosis of the Chudley-McCullough syndrome.

The first sister was 37-years old and was referred to our clinic because she had complaints about vague headaches that could not be further specified. She suffered from congenital bilateral sensorineural deafness, recurrent epilepsy and intellectual disability. She functioned at the level of a four- to six-year-old. The early motor development was only slightly delayed. As her sister, she had macrocephaly. She also had a painful feeling at the location of the valve of a previously implanted, but yet non-functional, ventriculo-atrial shunt. This shunt was implanted at the age of seven days due to a presumed hydrocephalus and had been revised three to four times according to her mother. The last revision had taken place before 1985 in her childhood. She was last seen in our clinic in the year 2000. Imaging at the time showed a complete disconnection of the shunt, but she had no complaints so the system was neither revised nor removed. MRI showed an asymmetrical enlarged occipital horn of the right lateral ventricle (colpocephaly) with the impression of an arachnoid cyst in the third ventricle without enlargement of the third and fourth ventricle (Figure 1A).

There was no aqueductal stenosis. The third ventricular recesses were not bulging and there was no sign of periventricular effusion. Furthermore, there was no cortical sulci and gyri effacement and there seemed to be enough extra-axial cerebrospinal fluid around the brain, which supports the absence of hydrocephalus. There was a partial agenesis of the corpus callosum, left cerebellar dysplasia, frontal polymicrogria, cerebellar dysgenesis, gray matter heterotopy, arachnoid cysts and sometimes mental retardation [8,9].

Until now, only forty cases have been described in literature [9]. Mutations in the G-protein signaling modulator 2 gene (GPSM2), which produces the Leu-Gly-Asn repeat-enriched protein (LGN), were found to be responsible for the syndrome [5]. Currently, nine different mutations in the GPSM2 gene are known to cause the Chudley-McCullough syndrome [2,4–6,9]. It has been suggested that GPSM2 has a role in maintaining cell polarity through effects on the orientation of the mitotic spindle, which is why a mutation may lead to aberrations in asymmetric cell divisions during development [5]. GPSM2 is widely expressed, amongst others on the apical surfaces of the hair and supporting cells of both the utricle and cochlea and in the saccul and cristae of the inner ear in mice [12], which explains the profound sensorineural hearing loss in Chudley-McCullough syndrome.

Here, we describe two new cases of Chudley-McCullough syndrome caused by a homozygous GPSM2 mutation in two adult sisters. To our knowledge, these are the eldest patients described with Chudley-McCullough syndrome so far. We emphasize the importance of determining the right diagnosis for patients with this rare syndrome, to prevent unneeded surgical interventions and to facilitate proper treatment.

Introduction

Chudley-McCullough syndrome, first described in 1997 [1], is a very rare autosomal recessive disorder characterized by partial corpus callosum agenesis, colpocephaly with a right-sided tendency and bilateral severe to profound sensorineural hearing loss [1–13]. Other abnormalities include cortical dysplasia, frontal polymicrogyria, cerebellar dysgenesis, gray matter heterotopy, arachnoid cysts and sometimes mental retardation [8,9].

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Here, we describe two new cases of Chudley-McCullough syndrome caused by a homozygous GPSM2 mutation in two adult sisters. To our knowledge, these are the eldest patients described with Chudley-McCullough syndrome so far. We emphasize the importance of determining the right diagnosis for patients with this rare syndrome, to prevent unneeded surgical interventions and to facilitate proper treatment.
of the lamina terminalis, because a third ventriculostomy was not feasible due to the fact that we could not clearly identify the corpora mamillaria and the bottom of the third ventricle was not transparent. Postoperatively and at follow-up, the local pain at the location of the former valve was gone but she still had occasional headaches, reflecting that the headaches were not caused by raised intracranial pressure or by an arachnoid cyst. The postoperative MRI after two months was unchanged (Figure 1B). Genetic testing showed homozygosity for the c.742del (p.(Gly249fs)) frameshift mutation in the \textit{GPSM2} gene and this genetically confirmed the diagnosis of Chudley-McCullough syndrome.

The second sister was 36-years old. Like her sister, she was intellectually disabled, had macrocephaly and functioned at about the same level as her sister. She also suffered from congenital bilateral sensorineural deafness and epilepsy. She has the same homozygous mutation in the \textit{GPSM2} gene. In the past she also had vague headaches without clear neurological deficit like her sister. MRI showed an asymmetrically enlarged right ventricle with an intraventricular arachnoid cyst (Figure 2A). There was also frontal polymicrogyria, gray matter heterotopia, cerebellar dysplasia and partial agenesis of the corpus callosum. At the time, the diagnosis Chudley-McCullough syndrome was not known and she was not tested for papilledema. There was no ataxia, which could hint at a mass effect of the cyst. Under the assumption of hydrocephalus as the cause of the ventriculomegaly and the headaches, a neurosurgical endoscopic procedure was performed without an apparent effect at the age of 22. During this exploration a large cyst wall was identified in the right lateral ventricle and fenestrated, followed by a third ventriculostomy. The postoperative MRI two weeks after surgery showed that the cyst was fenestrated, but the ventriculomegaly did not change (Figure 2B), suggesting that it was secondary to colpocephaly and not to a raised intracranial pressure. The patient reported a marginal improvement of the headaches, but they did persist. Recent control MRI 14 years after the operation showed an essentially unchanged size of the ventricles and the cyst was comparable to the first postoperative MRI (Figure 2C).

**Discussion**

Here we describe the two eldest known patients with Chudley-McCullough syndrome, both homozygous for the c742del (p.(Gly249fs)) frameshift mutation in the \textit{GPSM2} gene. Ancestors of the parents came from two very small nearby villages in the Netherlands (at about three km distance). Together with the detection of a homozygous mutation, this points to distant consanguinity of the parents. There has been debate in the literature about the terminology and the exact cause of the widened ventricles in Chudley-McCullough syndrome. Previously, the enlarged lateral ventricles were coined hydrocephalus several times, and it was thought to be caused by obstruction of the aqueduct \cite{7} or the foramen of Monroe \cite{1}. The available papers on the subject do not clearly describe whether there was a true hydrocephalus (for example the first case of Chudley et al. 1997 \cite{1}), but it is not a primary feature of the syndrome. The ventricular enlargement that is typically seen in this syndrome consists of asymmetrically enlarged...
occipital horns of the lateral ventricles, and is called colpocephaly. It is a congenital morphological malformation due to agenesis of the corpus callosum that causes a decreased structural integrity which may lead to dilatation of the lateral ventricles and brain atrophy [12,15]. Because the asymmetrical ventricles arise secondary to a developmental malformation and not a true hydrocephalus, surgical intervention will likely not relieve symptoms. Due to the presence of arachnoid cysts in Chudley-McCullough syndrome, this should also be differentiated from hydrocephalus.

In both sisters, it was difficult to get a good impression of the headaches because of their intellectual disability. The Diagnosis Chudley-McCullough syndrome was not made until after it was tried to resolve the headaches by attempting to treat the suspected hydrocephaly. It then became clear that they suffer from Chudley-McCullough syndrome and that their ventricular abnormalities fit with colpocephaly. The fourteen-year of stable follow-up in the second sister and our combined clinical and neurosurgical findings underscore this.

As in our cases, many authors were tempted to operate the “hydrocephalus” in patients with Chudley-McCullough syndrome, most often with a ventriculoperitoneal shunt [1,5,9,10,12,13,16] and in many cases without a clear effect. Other authors also noted that treatment of the ventricular enlargement through shunting or fenestration of the cyst had no effect [12,16]. Therefore, we believe no neurosurgical intervention is required in patients with Chudley-McCullough syndrome, unless there is clear evidence of raised intracranial pressure.

Conclusion

Chudley-McCullough syndrome is a very rare developmental disorder, characterized amongst others by colpocephaly and arachnoid cysts. The colpocephaly may be mistaken for hydrocephalus, but it is secondary to a congenital morphological malformation and not caused by raised intracranial pressure. We believe no neurosurgical intervention is required in patients with Chudley-McCullough syndrome, unless there is clear evidence of raised intracranial pressure indicating a symptomatic hydrocephalus.

Conflict of Interest

The authors declare that they do not have conflicts of interest.

References


*Corresponding author: Adriaan RE, Potgieser, Department of Neurosurgery, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30.001, 9700 RB Groningen, The Netherlands, Tel: +31-503-615-657; Fax: +31-503-615-715; E-mail: a.r.e.potgieser@umcg.nl.

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