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Surprisingly good outcome in antenatal diagnosis of severe hydrocephalus related to *CCDC88C* deficiency

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ABSTRACT

Non-syndromic congenital hydrocephalus is aetiologically diverse and while a genetic cause is frequently suspected, it often cannot be confirmed. The most common genetic cause is *L1CAM*-related X-linked hydrocephalus and that explains only 5%–10% of all male cases. This underlines a current limitation in our understanding of the genetic burden of non-syndromic congenital hydrocephalus, especially for those cases with likely autosomal recessive inheritance. Additionally, the prognosis for most cases of severe congenital hydrocephalus is poor, with most of the surviving infants displaying significant intellectual impairment despite surgical intervention. It is for this reason that couples with an antenatal diagnosis of severe hydrocephalus are given the option, and may opt, for termination of the pregnancy. We present two families with *CCDC88C*-related recessive congenital hydrocephalus with children who had severe hydrocephalus. Those individuals who were shunted within the first few weeks of life, who did not require multiple surgical revisions, and who had a more distal truncating variant of the *CCDC88C* gene met their early childhood developmental milestones in some cases. This suggests that children with *CCDC88C*-related autosomal recessive hydrocephalus can have normal developmental outcomes under certain circumstances. We recommend *CCDC88C* analysis in cases of severe non-syndromic congenital hydrocephalus, especially when aqueduct stenosis with or without a medial diverticulum is seen, in order to aid prognosis discussion.

1. Introduction

Congenital hydrocephalus has an estimated prevalence of approximately 1/1000 (Jeng et al., 2011; Munch et al., 2012). It may be due to secondary (extrinsic) causes such as intracranial hemorrhages, intrauterine infections, neural tube defects, tumours, teratogens or trauma and it can also be a primary (intrinsic) disorder, subdivided into those with (syndromic) and those without (non-syndromic) major clinical features outside the brain. Severe non-syndromic primary congenital hydrocephalus has a high perinatal mortality rate and poor prognosis with approximately 90% of surviving infants displaying neurological and physical disability (Levitsky et al., 1995; Breeze et al., 2007; Kennelly et al., 2009). The underlying aetiology is often not clear and it is therefore unsurprising that a significant proportion of parents may opt to terminate an affected pregnancy (Garne et al., 2010; Hannon et al., 2012). Most cases of primary non-syndromic hydrocephalus unrelated to a myelomeningocele are due to aqueduct obstruction (Tully et al., 2015; Adle-Biassette et al., 2013), and the hydrocephalus associated with aqueduct obstruction tends to be early in onset, of greater severity and associated with worse developmental outcomes compared to other forms of hydrocephalus (Tully et al., 2015).

The pattern of family aggregation and the increasing recurrence risk ratios in individuals with a closer genetic relationship supports the involvement of a genetic component in the aetiology of primary congenital hydrocephalus (Munch et al., 2012). It is important to identify if

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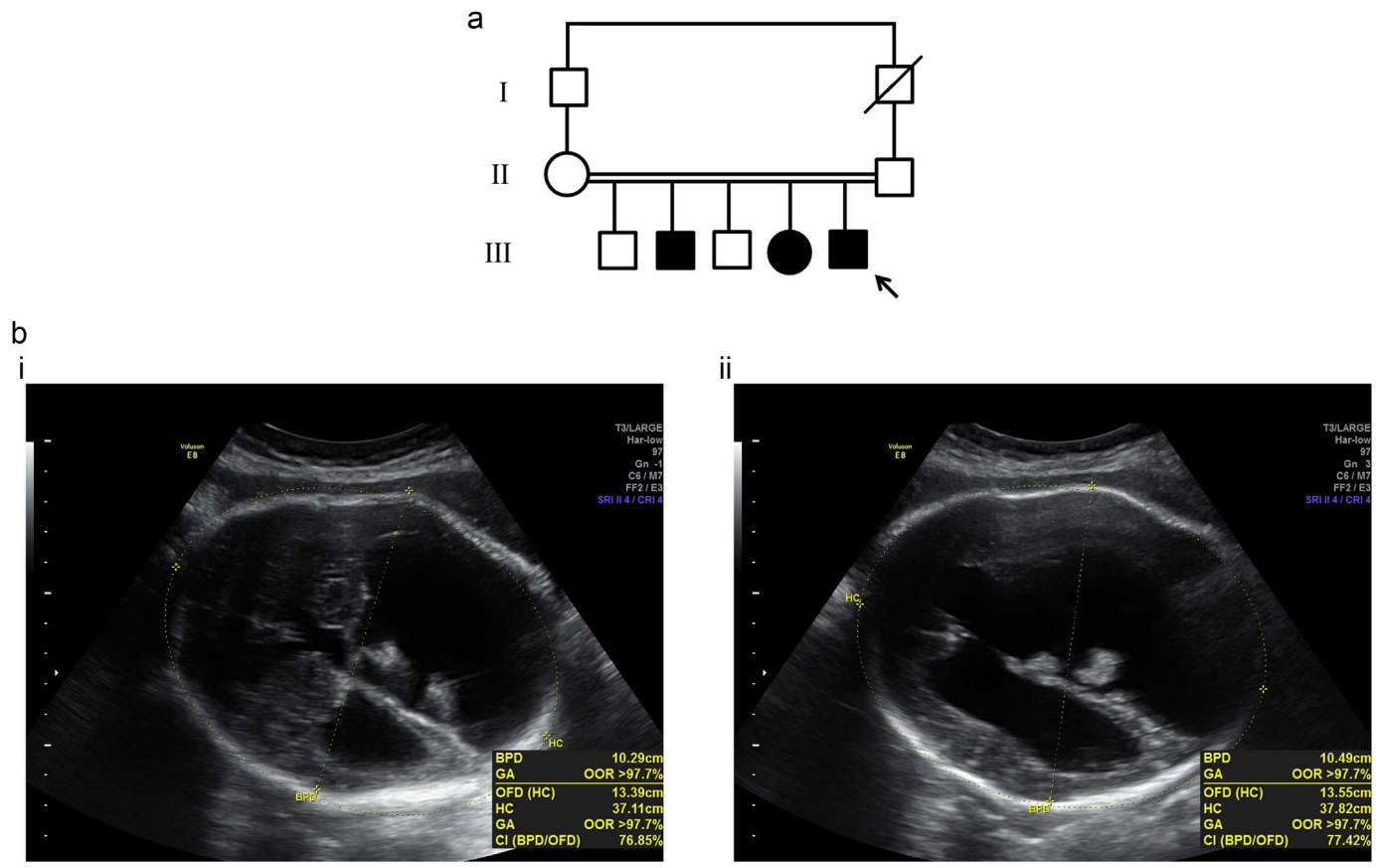

Fig. 1. a. Family 1. b. Antenatal USS images. Patient 3 at 34 weeks gestation.

a specific genetic condition can be recognised for anyone with primary congenital hydrocephalus for an accurate diagnosis, prognosis and to aid genetic counselling. The magnetic resonance imaging (MRI) findings can be particularly useful and can help detect subtle but potentially distinguishable conditions such as muscle-eye-brain (MEB) disease, forms of lissencephaly and *AP1S2*-associated hydrocephalus; however, a specific genetic condition is only recognised using imaging and clinical findings in a minority of patients (Tully and Dobyns, 2014). Genetic testing is non-diagnostic in most instances of non-syndromic congenital hydrocephalus, with L1 syndrome due to pathogenic variants in the X-linked *L1CAM* gene the most commonly identified genetic cause and accounting for 5%–10% of all male cases (Tully et al., 2015; Finckh et al., 2000; Verhagen et al., 2011). In patients with multiple clinical characteristics of L1 syndrome and a positive family history, pathogenic or likely pathogenic variants in *L1CAM* can be seen with a frequency as high as 85% (Vos et al., 2010); however, L1 syndrome may or may not present with distinguishing features such as adducted thumbs, and testing should be performed in all males with non-syndromic hydrocephalus.

The empiric recurrence risk for congenital hydrocephalus, excluding X-linked hydrocephalus, has been estimated to be approximately 1–4% (Verhagen et al., 2011; Schrander-Stumpel and Fryns, 1998). A significant proportion of patients referred for *L1CAM* gene analysis with no subsequent pathogenic variant identified may show signs of an autosomal recessive mode of inheritance (Adle-Biassette et al., 2013) and autosomal recessive inheritance has been implicated as a likely pattern of inheritance for many cases of familial congenital hydrocephalus (Haverkamp et al., 1999; Lapunzina et al., 2002; Addar and Babay, 2004; Vanlieferinghen et al., 1987; Barros-Nunes and Rivas, 1993; Brady et al., 1999). Shaheen et al. (2017) found a likely causal autosomal recessive variant in sixteen different genes in the majority of families with recurrence of congenital hydrocephalus (21 of 27; 78%) (Shaheen et al., 2017). No pathogenic or likely pathogenic *L1CAM, CCDC88C* or X-linked gene variants were found in their study population, and the conditions they identified were principally syndromic forms of familial congenital hydrocephalus, such as dystroglycanopathies and ciliopathies (Shaheen et al., 2017).

CCDC88C-related autosomal recessive non-syndromic hydrocephalus is a rare condition and it has been reported in just three families with severe non-syndromic hydrocephalus due to aqueduct stenosis (Ekici et al., 2010; Drielsma et al., 2012). There was one previously reported individual with *CCDC88C*-related hydrocephalus who was said to have normal development at three years of age after antenatal diagnosis of severe hydrocephalus (Ekici et al., 2010). In this paper, we provide clinical detail on additional children with severe *CCDC88C*-related hydrocephalus, some of whom also had normal development, and we sought to clarify what features might be associated with better neurocognitive outcome in these patients.

2. Patient data and methods

2.1. Family 1

2.1.1. Patient 1

Patient 1 is the second child born to a consanguineous Saudi couple (Fig. 1a). He had a ventriculoperitoneal (VP) shunt placed at two months of age due to hydrocephalus and a left-sided occipital porencephalic cyst. The shunt was revised soon after insertion due to infection, but no further revisions were required. He had a history of mild gross motor and speech delay and on examination at age seven, he had plagiocephaly with a head circumference of 52.5 cm (+0.31 standard deviations (SD)). He had a normal comparative genomic hydridization (aCGH) oligonucleotide microarray (Agilent 180k), normal standard G-banded karyotype at a resolution of 500 bands per haploid set and