The genetic basis of human hydrocephalus

Hindbrain development, growth regulation and more

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and

Seattle Children's
The genetic basis of hydrocephalus

• Simple inheritance
  ▫ AD, AR and XL disorders
  ▫ Chromosome disorders

• Developmental disorders
  ▫ Neural tube disorders
  ▫ Forebrain DEV disorders
  ▫ Mid-hindbrain DEV disorders
  ▫ Brain growth disorders
  ▫ Cortical malformations

• The CSF system
  ▫ Choroid plexus, ependyma
  ▫ Aqueduct and SCO
  ▫ Ventricles and foramina
  ▫ Extra-axial space and “AG”

• Genes and pathways
  ▫ Early pattern formation
    ▪ SHH, ZIC2, other HPE genes
    ▪ FOXC1, ZIC1/4, DWM genes
    ▪ Pax6, Wnt1
    ▪ Msi1, Msx1, Rfx4
  ▫ Neuronal pathfinding
    ▪ L1CAM
  ▫ Cortical development
    ▪ POMT1 and many COB gene
  ▫ Growth regulation
    ▪ PIK3CA, PIK3R2, AKT3

• Where do you start?
The scope of the problem for HYD

- Prenatal HYD
  - N = 286 fetuses
    - 30% (82/286) die
    - 29% (80/286) have intellectual disability
    - 41% (114/286) are normal
The scope of the problem for HYD

- **Congenital HYD**
  - \( N = 48 \) children
    - 33% (16/48) die
    - 19% (09/48) have intellectual disability
    - 48% (23/48) are normal or have mild LD
Inheritance of HYD

- **Single gene disorders**
  - AD
    - No human genes
  - AR
    - No human genes
  - XL
    - L1CAM
- **Chromosome disorders**
  - 6p25.3
  - 6q25.3-qter
  - 8q12.2-q21.2
  - Others
Letter to the Editor

Autosomal Recessive Nonsyndromal Hydrocephalus

To the Editor:

The report of Willemsa et al. [1987] on a large kindred with an unusual form of X-linked hydrocephalus without aqueductal stenosis is very interesting and prompts us to describe a consanguineous Arab family with four hydrocephalic children (two males, and two females), one confirmed at autopsy to have the Arnold-Chiari malformation. This family may indicate the existence of an autosomal recessive form, adding further evidence for genetic heterogeneity of familial hydrocephalus.

CLINICAL REPORTS

Family Data (Fig. 1)

The father and mother (III-7 and III-8) were phenotypically normal first cousins of Palestinian Arab origin. They were 35 and 27 years old, respectively, when evaluated in 1983. They have a normal daughter (IV-1) born in 1977 and another (IV-2), who died in infancy from bronchopneumonia. The third child (IV-3) was a male stillborn at term by cesarean section (CS) with hydrocephalus documented from files, with occipitofrontal circumference (OFC) of 42 cm and weight of 3.400 g, with no other reported anomalies.

Patient 1 (IV-4)

A female, the second affected hydrocephalic sib, was born in August 1983 at term. The mother received daily folate acid supplements for 3 months in the preconception and early conception periods. Hydrocephaly was diagnosed prenatally by real-time ultrasound, which showed a progressive increase in the head circumference from the 19th week but, because of religious beliefs, the mother did not wish to terminate the pregnancy, which ended spontaneously at term. CS was done because of cephalopelvic disproportion and shoulder presentation. At birth, the infant showed an apparent hydrocephalus by transillumination with widely open sutures. OFC was 41 cm and weight was 3.250 g.

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XL-HYD and L1CAM

**MUTATION UPDATE**

Genetic and Clinical Aspects of X-linked Hydrocephalus, Assimilation of Atypical Lesions

- XL-HYD with AQ stenosis
  - 25% of males with isolated HYD
  - Severe HYD, prenatal onset
  - Adducted thumbs, defect of extensor pollicus (>50%)
  - Spasticity
  - Severe ID

- MASA syndrome
- SPG1 (spastic paraplegia)
- XL complicated ACC

- Loss of cell adhesion and intracellular signalling

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**Mutations**

- **Find Mutations**
  - Exon/intron: All
  - Reported classification: All classifications
  - Type: All types
  - Results per page: 20

**Mutations Table**

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<th>DNA change</th>
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XL-HYD and \textbf{L1CAM}

- **L1CAM (L1 cell adhesion molecule)**
  - Immunoglobulin-like family of cell-adhesion glycoproteins
  - Highly conserved
  - Expressed in neurons throughout the brain during development
  - Controls many processes
    - Neurite outgrowth
    - Axonal guidance
    - Synaptogenesis
    - Myelination
    - Fasciculation
  - Regulated by MAPK pathway, which phosphorylate the protein and modulates its interaction with ankyrin B
Genetics of HYD

Genetic testing (clinical labs)

- Most patients with HYD
  - Chromosome microarray
  - L1CAM sequencing and dup/del analysis

- Syndromes
  - Testing selected for the specific syndrome suspected

Recurrence risk data

- Male proband
  - 12 - 15%

- Female proband
  - 05 - 06%
HYD in developmental brain disorders

- Neural tube disorders
  - Myelomeningocele
  - Cephaloceles
- Forebrain DEV disorders
  - Holoprosencephaly
  - Corpus callosum agenesis
- Mid-hindbrain DEV disorders
  - Dandy-Walker spectrum
  - Rhombencephalosynapsis
  - Pontine tegmental cap dysplasia
  - Others
- MCD: brain growth
  - Microcephaly (rare)
  - Megalencephaly
- MCD: neuronal migration
  - Heterotopia
  - Lissencephaly
  - Cobblestone malformation
- MCD: post-migrational
  - Polymicrogyria
Hydrocephalic holoprosencephaly: An oxymoron? Insights into etiology and management

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Abstract

Holoprosencephaly is usually associated with microcephaly, although macrocephaly is not uncommonly seen. However, the cause of hydrocephalus in holoprosencephaly remains ill-defined. Here, the authors report a case of CSF ascites following ventriculoperitoneal shunt placement in a five-month-old child with alobar holoprosencephaly, and hypothesize that the excessive CSF production which occurs in this condition may be responsible for the formation of CSF ascites. Further research is required to assess whether the gene responsible for holoprosencephaly is also responsible for upregulating CSF production in patients with concomitant hydrocephalus.

Keywords: Complication, CSF ascites, holoprosencephaly, hydrocephalus, shunt

SHH, SIX3, ZIC2, ~15 others
ACC/cysts and HYD

- Type I cysts communicates with LV
  - Ia with frequent HYD
  - Ib with frequent HYD
- Type 2 no communication with LV
  - IIa with frequent HYD (M>F)
  - IIb with frequent HYD (Aicardi)

Callosal agenesis with cyst
A better understanding and new classification
A. James Barkovich, MD; Erin M. Simon, MD; and Christopher A. Walsh, MD, PhD

Article abstract—Objective: To analyze imaging studies of 25 cases of agenesis of the corpus callosum with interhemispheric cyst to assess this malformation itself and associated anomalies. Methods: CT (6 patients) and MRI (19 patients) were retrospectively reviewed. The patients were categorized according to morphologic and clinical characteristics. Results: Based on morphology, the patients were separated into two major types, each with subtypes. Type 1 cysts appear to be an extension or diverticulum of the third or lateral ventricles, whereas Type 2 are localized and do not communicate with the ventricular system. Type 1a were associated with periventricular hydrocephalus but no other cerebral malformations. Type 1b were associated with hydrocephalus secondary to disconnection malformations prohibiting egress of CSF from the third ventricle into the aqueduct of Sylvius. Type 1e were associated with small head size and apparent cerebral hemispheric dysplasia or hypoplasia. Type 2a (callosal cysts) were associated with neurodevelopmental disorders other than callosal agenesis/hygrophysis. Type 2b were associated with deficiencies of the falx cerebri, subependymal heterotopia, and polymicrogyria (and were almost all in patients diagnosed with Aicardi syndrome). Type 2e were associated with subcortical heterotopia. Type 2d consists of interhemispheric arachnoid cysts. Other than those with Type 2b cysts, gender predominance was overwhelmingly male. Conclusion: Agenesis of the corpus callosum with interhemispheric cyst appears to consist of a heterogeneous group of disorders that have in common callosal agenesis and extracallosal cysts, both of which are among the commonest CNS malformations. This article proposes a classification system, based primarily on morphology, by which this complex group of disorders might begin to be better understood.

Neurol 2001;66:229–235

The ability of MRI to show the gross morphology of the brain in vivo using thin sections in multiple planes has allowed the identification of previously unknown malformations, a new appreciation of the frequency of malformations that were previously thought extremely rare, and differentiation of malformations that were previously combined. Although MRI has been utilized to assess the agenesis/hydrocephaly with seizures in 1 patient, microcephaly with infantile spasms in 1 patient, and partial motor seizures with right spastic hemiparesis in 1 patient.

Imaging consisted of MRI in 17 patients, X-ray CT in 6, and both MR and CT in 2. MR studies varied in sequence; all were performed at multiple institutions over a period of 16 years. However, all studies included sagittal T1 images, axial T2-weighted images, and coronal T1- or T2-weighted images. All CT scans included both axial and coronal images, although in three patients the cerebral images were reformatted from 5-mm-thick axial sections. Paramagnetic contrast was administered in five of the MR scans and iodinated contrast was administered in two of the CT scans.

All of the scans were reviewed with particular attention to the degree of callosal abnormality (agenesis versus hypoplasia, severity of hypoplasia, character of the cyst (unilocular versus multilocular, intensity or attenuation as compared to CSF of the ventricles and subarachnoid space, location, communication with the ventricular system), and the presence and type of associated malformations. Clinical information was limited, as most of the patients were imaged as neonates because of microcephaly or ultrasound findings of ventricular enlargement or cyst. When information from later in infancy or childhood was available, it was examined to determine neurologic status, developmental status, the presence or absence of seizures, type of seizures, and whether any anomalies were present outside of the nervous system. Based on these characteristics and...
Disruption of the murine nuclear factor I-A gene (Nfia) results in perinatal lethality, hydrocephalus, and agenesis of the corpus callosum

- Phenotype
  - Intellectual disability, ACC, HYD or VMEG
  - Chiari 1, tethered cord
  - Urinary tract anomalies
- Gene
  - Nuclear Factor I (NFI) family of transcription factors

NFIA Haploinsufficiency Is Associated with a CNS Malformation Syndrome and Urinary Tract Defects

ACC and HYD or VMEG

Tethered cord and urinary tract anomalies
FOXC1, ZIC1 and ZIC4

FOXC1 is required for normal cerebral development and is a major contributor to chromosome 6p25.3 Dandy-Walker malformation

Kimberly A Aldinger¹, Orden J Lehmann², Louise K Hodson³, Victor Y Chิดziko⁴, Alexander G Bassuk⁵, Lesley C Adey⁶, Ian D Krantz⁷, William B Dobyns⁸,9 & Kathleen J Miller¹,4,5

Dandy-Walker malformation (DWM), the most common human cerebellar malformation, has only one characterized associated locus². Here we characterize a second DWM-linked locus on 6p25.3, showing that deletions or duplications encompassing FOXC1 are associated with cerebellar and posterior fossa malformations including cerebellar vermis hypoplasia (CVH), mega-cisterna magna (MCM) and DWM. Foxtail-/- mice have embryonic abnormalities of the thymic tip due to loss of mesenchyme-secreted signaling molecules with subsequent loss of notch expression in thymus. FOXC1 homozygous hypomorphic have CVH with medial fissure and foliation defects. Human FOXC1 heterozygous mutations are known to affect eye development, causing a spectrum of glabelenoskeletal anomalies (Aarskog-Düren syndrome, AARS; MIM no. 606035). We report the first brain imaging data from humans with FOXC1 mutations and show that these individuals also have CVH. We conclude that alteration of FOXC1 function alone causes CVH and contributes to MCM and DWM. Our results highlight a previously unrecognized role for mesenchyme-neuromere interactions in the mid-hindbrain during early embryogenesis.

Malformations of the cerebellum are common, heterogeneous human birth defects with chromosomal, single-gene and complex etiologies¹. CVH, MCM and DWM are generally classified as separate disorders, but they overlap in appearance, and it remains unclear whether they represent distinct entities or share a common pathogenesis². We found reports supporting four classic DWM-associated loci, including chromosome 15p15.2 and 15q11-q13, with high resolution genotyping (Supplementary Table 1). We
Rhombencephalosynapsis: review of brain imaging 42 patients
- HYD in 45% (19/42)
- Links to VACTERL-H and maternal DM
- Congenital obstructive HYD
- RES in 9%