Table 1 Classification of patients with CHI and AS [*ar* autosomal recessive, *X-li* X-Linked, (*r*) right, (*l*) Left]

Patient no.	Classified as	Clinical characteristics	Family history	Assumed mode of inheritance	Recurrence risk
1	Familial	Male infant, on term, adducted thumbs	CHI in maternal nephew and maternal grandfather	X-li	50% for male sibs
2	Familial	Male preterm infant (35 weeks, spontaneous delivery)	Two maternal nephews 2° and one brother with CHI, one abortion of mother	X-li	50% for male sibs
3	Familial	Male infant, on term, adducted thumbs	Consanguineous parents, brother of patient 4	ar	25%
4	Familial	Male infant, on term, adducted thumbs	Consanguineous parents, sister of patient 3	ar	25%
5	Sporadic	Male infant, on term, adducted thumbs	–	–	–
6	Sporadic	Male infant, on term, adducted thumbs	–	–	–
7	Sporadic	Male infant, on term, adducted thumbs	–	–	–
8	Sporadic	Male infant, on term, adducted thumbs	–	Multifactorial	3–4%
9	Sporadic	Male infant, on term, adducted thumbs	–	–	0–3%
10	Sporadic	Male infant, on term, adducted thumbs	–	ar	25%
11	Sporadic	Male infant, on term, adducted thumbs	–	ar, X-li	25% (50% for male sibs)
12	Sporadic	Male infant, on term, adducted thumbs	–	ar, X-li	25% (50% for male sibs)
13	Sporadic	Male infant, on term, adducted thumbs	–	ar	25%
14	Sporadic	Male infant, on term, adducted thumbs	–	ar	25%
15	Sporadic	Male infant, on term, adducted thumbs	–	X-li (possibly ar), because syndrome cannot be excluded	Up to 25%
16	Sporadic	Male infant, on term, adducted thumbs	–	X-li (possibly ar), because syndrome cannot be excluded	Up to 25%
17	Sporadic	Male infant, on term, adducted thumbs	Mother's brother died due to hydrocephalus	X-li (possibly ar), because syndrome cannot be excluded	Up to 25%
18	Sporadic	Male infant, on term, adducted thumbs	–	X-li (possibly ar), because syndrome cannot be excluded	Up to 25%
19	Sporadic	Male infant, on term, adducted thumbs	–	Unspecified	<2% (see text)
20	Sporadic	Male infant, on term, adducted thumbs	–	Unspecified	4% (see text)

Eur J Pediatr (1999) 158: 474–478

MEDICAL GENETICS

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Congenital hydrocephalus internus and aqueduct stenosis: aetiology and implications for genetic counselling

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Abstract Genetic counselling in families with congenital hydrocephalus internus (CHI) in combination with aqueduct stenosis (AS) is often difficult due to an uncertain aetiology. We present a series of 35 patients with CHI and AS focusing on the aetiology and presumed recurrence risk for siblings. In 13 patients (37.1%) a genetic aetiology was identified with an increased recurrence risk for siblings. The relative frequency of patients with X-linked hydrocephalus in our sample was in accordance with the literature (2/35), but was more frequent in other diseases with Mendelian inheritance.

Conclusion In addition to the well-known X-linked and autosomal recessive forms of aqueduct stenosis with hydrocephalus, this malformation can occur in other diseases with Mendelian inheritance. This finding is of considerable importance for genetic counselling and prognosis.

Key words Congenital internal hydrocephalus · Aqueduct stenosis · Inheritance · Aetiology · Genetic counselling

Abbreviations *AS* aqueduct stenosis · *CHI* congenital hydrocephalus internus · *XLC* X-linked congenital hydrocephalus internus

Introduction

The frequency of congenital hydrocephalus internus (CHI) varies between 0.5 and 2.5 per 1000 newborns for different populations [4, 11, 13, 22, 25]. Retrospective studies report a low overall recurrence risk (0.6–1.4%) of CHI [4, 7].

In 22.5–42.9% of patients, CHI is associated with aqueduct stenosis (AS) [4, 13]. The most common causes of AS are intra-uterine infections or intracerebral haemorrhage. There are also cases compatible with Mendelian inheritance [4]. The most common monogenetic type with a frequency of 4.5–14.2% is X-linked CHI (XLC) [4, 13, 20]. In male patients with CHI and AS, it is assumed that XLC may be present in up to 23%–25% [4, 13]. The overall recurrence risk for male siblings of a male index patient has been reported to be about 12%; for female siblings the recurrence risk is 2%–6% [4, 13]. If the index patient is female, the empiric recurrence risk is usually 2% or less, indicating that autosomal-recessive inheritance is rare [2, 5, 13, 14, 23]. However, specific subgroups of infants with CHI bear a higher recurrence risk, e.g. in patients suffering from a specific genetic disease [1]. With respect to the underlying aetiology, epidemiological data on patients with CHI and AS are lacking. The aim of our study was to determine the specific aetiology as well as the relative frequency of conditions leading to CHI and AS in a series of 35 patients.

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Congenital HYD: other causes

OBSTETRICS

Diabetes mellitus and birth defects

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OBJECTIVE: The purpose of this study was to examine associations between diabetes mellitus and 39 birth defects.

STUDY DESIGN: This was a multicenter case-control study of mothers of infants who were born with (n = 13,030) and without (n = 4895) birth defects in the National Birth Defects Prevention Study (1997-2003).

RESULTS: Pregestational diabetes mellitus (PGDM) was associated significantly with noncardiac defects (isolated, 7/23 defects; multiples, 13/23 defects) and cardiac defects (isolated, 11/16 defects; multiples, 8/16 defects). Adjusted odds ratios for PGDM and all isolated and multiple defects were 3.17 (95% CI, 2.20-4.99) and 8.62 (95% CI, 5.27-14.10), respectively. Gestational diabetes mellitus (GDM) was associated with fewer noncardiac defects (isolated, 3/23 defects; multiples, 3/23 defects) and cardiac defects (isolated, 3/16 defects; multiples, 2/16 defects). Odds ratios between GDM and all isolated and multiple defects were 1.42 (95% CI, 1.17-1.73) and 1.50 (95% CI, 1.13-2.00), respectively. These associations were limited generally to offspring of women with prepregnancy body mass index ≥25 kg/m^2.

CONCLUSION: PGDM was associated with a wide range of birth defects; GDM was associated with a limited group of birth defects.

Key words: birth defect, gestational diabetes mellitus, obesity, pregestational diabetes mellitus

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Birth defects affect 1 in 33 babies and are a leading cause of infant death in the United States.[1,2] The causes of most birth defects remain unknown.[3,4] Although pregestational diabetes (PGDM; ie, type 1 or type 2) is a known risk factor for defects of the cardiovascular, central nervous, musculoskeletal systems, on the specific phenotypes within each of these organ systems that are associated with diabetes mellitus remains unclear because most published studies have examined broad categories of birth defects. Moreover, the effect of diabetes mellitus on other organ systems

Although the mechanisms underlying the associations of diabetes mellitus with birth defects are not understood completely, it is clear that hyperglycemia plays a critical role. There is a positive correlation between hyperglycemia during embryogenesis and a risk for congenital birth defects that are associated with PGDM has been glycemic control during pregnancy.[14] However, the increasing prevalence of diabetes mellitus[15] and the challenges in achieving adequate glycemic control periconceptionally among women with diabetes mellitus[16] raise concerns about the extent to which PGDM contributes to the burden of birth defects in the United States today.

Gestational diabetes mellitus (GDM) has also been reported as being associated with birth defects.[5,17] Because some women diagnosed with GDM for the first time actually may have undiagnosed

From the Division of Birth... Control and Prevention, ... Ms Besser); the Departme... City, UT (Dr Botto); the ... of Arkansas for Medical S... Rock, AR (Drs Hobbs and Cleves); the School of Public Health, University of Texas Health Science Center at Houston, Houston, TX (Dr Waller); and the University of Maryland School of Medicine, Baltimore, MD (Dr Reece).

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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TABLE 2
Adjusted ORs[a] and 95% CIs for associations between diabetes mellitus and selected noncardiac birth defects: NBDPS, 1997-2003

	Pregestational (type 1 or type 2) diabetes mellitus				GDM			
	Isolated defects		Multiple defects		Isolated defects		Multiple defects	
Birth defect	Exposure odds[b]	OR (95% CI)	Exposure odds[b]	OR (95% CI)	Exposure odds[b]	OR (95% CI)	Exposure odds[b]	OR (95% CI)
Control subjects	24/4689		24/4689		182/4689		182/4689	
All noncardiac defects	75/6162	2.34 (1.44-3.81)	62/1233	7.80 (4.66-13.05)	209/6162	1.30 (1.05-1.60)	68/1233	1.31 (0.95-1.80)
Anencephaly and craniorachischisis	4/216	3.39 (1.11-10.31)	0/20	NE	10/216	1.33 (0.68-2.61)	1/20	1.63 (0.20-13.11)
Spina bifida	2/444	0.75 (0.17-3.24)	2/43	7.99 (1.61-39.70)	28/444	1.21 (0.74-1.96)	1/43	0.70 (0.09-5.22)
Encephalocele	3/73	2.09 (0.26-16.56)	0/25	NE	5/73	1.82 (0.70-4.71)	0/25	NE
Holoprosencephaly	1/41	6.00 (0.72-49.76)	1/18	16.16 (1.59-163.88)	1/41	0.76 (0.10-5.75)	0/18	NE
Hydrocephaly	6/146	8.80 (3.39-22.84)	6/53	12.13 (3.68-39.98)	10/146	1.97 (0.96-4.03)	4/53	1.86 (0.63-5.47)
Anotia/microtia	5/193	3.75 (1.04-13.51)	7/66	18.50 (6.95-49.24)	13/193	1.31 (0.65-2.61)	2/66	0.43 (0.06-3.20)
Choanal atresia	1/35	5.43 (0.63-47.09)	0/29	NE	3/35	1.67 (0.38-7.28)	2/29	2.20 (0.49-9.92)
Cleft palate	5/535	1.80 (0.67-4.87)	6/119	10.73 (3.99-28.86)	29/535	1.54 (1.01-2.37)	5/119	1.26 (0.50-3.20)
Cleft lip with or without cleft palate	14/1066	2.92 (1.45-5.87)	8/139	8.07 (3.05-21.39)	54/1066	1.45 (1.03-2.04)	8/139	1.22 (0.52-2.86)
Small intestinal atresia	0/165	NE	0/25	NE	5/165	0.45 (0.14-1.46)	4/25	3.59 (0.99-12.98)
Duodenal atresia	0/54	NE	0/30	NE	1/54	0.51 (0.07-3.79)	5/30	4.19 (1.40-12.59)
Esophageal atresia	0/127	NE	6/188	7.04 (2.69-18.45)	9/127	1.57 (0.67-3.69)	6/188	1.05 (0.45-2.43)
Anorectal atresia	4/200	4.70 (1.55-14.26)	11/230	8.22 (3.62-18.66)	14/200	1.91 (1.02-3.56)	14/230	1.41 (0.74-2.69)
Biliary atresia	1/65	3.14 (0.40-24.62)	1/14	18.40 (1.84-183.79)	5/65	2.21 (0.85-5.75)	0/14	NE
Hypospadias	8/806	1.89 (0.70-5.14)	6/70	18.73 (5.59-62.76)	38/806	1.49 (0.94-2.37)	8/70	2.94 (1.14-7.61)
Bilateral renal agenesis/hypoplasia	3/47	11.91 (3.10-45.72)	1/20	NE	1/47	0.58 (0.08-4.32)	0/20	NE
Longitudinal limb	3/109	6.47 (1.83-22.90)	4/86	7.01 (1.91-25.68)	7/109	1.82 (0.77-4.29)	3/86	0.94 (0.29-3.09)
Sacral agenesis/caudal dysplasia	1/3	NE	10/18	130.17 (33.80-501.40)	0/3	NE	0/18	NE

NE, not estimable from the logistic regression model.

[a] Models adjusted for maternal age, race/ethnicity, entry into prenatal care, BMI, study center, and household income.

[b] Ratio of number of cases (or control subjects) with diabetes mellitus to the number of cases (or control subjects) without diabetes mellitus of any type.

Correa. Diabetes mellitus and birth defects. Am J Obstet Gynecol 2008.

Holoprosencephaly 1/41 6.00 (0.72-49.76) 1/18 16.16 (1.59-163.88) 1/41 0.76 (0.10-5.75) 0/18 NE
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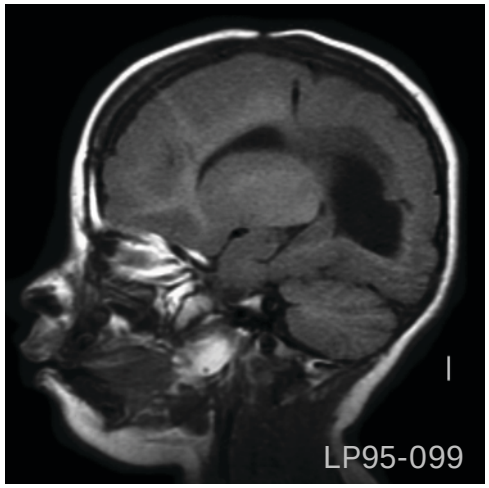
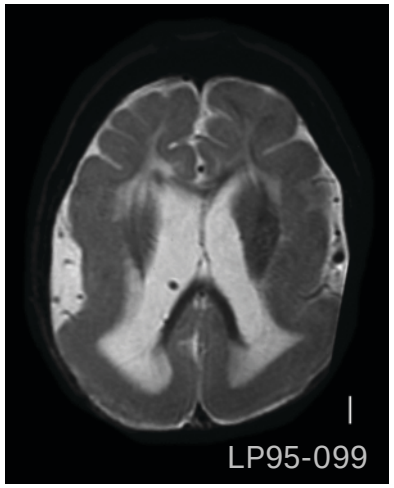
analyzed: 7 of 23 isolated noncardiac defects and 11 of 16 isolated cardiac defects; 13 of 23 multiple noncardiac defects and 8 of 16 multiple cardiac defects. These associations tended to be stronger when the defect that was studied occurred with other defects (multiple) rather than as an isolated defect. GDM was associated with 3 of 23 isolated noncardiac defects and 3 of 16 isolated cardiac defects and with 3 of 23 multiple noncardiac defects and 2 of 16 multiple cardiac defects. The associations with GDM were weaker and generally limited to offspring of women with a prepregnancy BMI ≥25.0 kg/m^2.

Strengths of this study include the large sample size and standardized procedures for case definition and classification of birth defects, which allowed for examination of more specific categories of birth defects than has been possible in previous studies. The study's ability to characterize the current impact of

LIS and HYD





- Lissencephaly and HYD
  - HYD in 1-2% of children with classic LIS
  - HYD in 5% of Lis1 knockout mouse
  - *LIS1*$^{+/-}$ or *Lis1*$^{-/-}$ in mouse

- This boy has classic LIS due to deletion 17p13.3 including the LIS1 gene (aka PAFAH1B1). The small black "dot" in the RLV on the axial image is a shunt. The parasagital image also shows the shunt.

article

Graded reduction of *Pafah1b1 (Lis1)* activity results in neuronal migration defects and early embryonic lethality

Shinji Hirotsune[1,5], Mark W. Fleck[2], Michael J. Gambello[1], Gregory J. Bix[3], Amy Chen[1], Gary D. Clark[3], David H. Ledbetter[4], Chris J. McBain[2] & Anthony Wynshaw-Boris[1]

Heterozygous mutation or deletion of the β subunit of platelet-activating factor acetylhydrolase (*PAFAH1B1*, also known as *LIS1*) in humans is associated with type I lissencephaly, a severe developmental brain disorder thought to result from abnormal neuronal migration. To further understand the function of *PAFAH1B1*, we produced three different mutant alleles in mouse *Pafah1b1*. Homozygous null mice die early in embryogenesis soon after implantation. Mice with one inactive allele display cortical, hippocampal and olfactory bulb disorganization resulting from delayed neuronal migration by a cell-autonomous neuronal pathway. Mice with further reduction of *Pafah1b1* activity display more severe brain disorganization as well as cerebellar defects. Our results demonstrate an essential, dosage-sensitive neuronal-specific role for *Pafah1b1* in neuronal migration throughout the brain, and an essential role in early embryonic development. The phenotypes observed are distinct from those of other mouse mutants with neuronal migration defects, suggesting that *Pafah1b1* participates in a novel pathway for neuronal migration.

Introduction

As a result of highly ordered neuronal migration during development, several regions of the adult brain become organized into laminar structures[1,2]. For example, the adult cerebral cortex consists of six neuronal layers (I–VI). These layers are formed from an outward migration of post-mitotic neurons that arise from mitotic progenitor neuroblasts in the germinal zone adjacent to the ventricles[3,4], guided for the most part by radial glial fibers that stretch from the ventricle to the pial surface[5,6]. The earliest cells arriving in the cortical plate eventually become the deepest layer (VI) of the cortex, and the remaining cortical layers are laid down sequentially in an inside-out fashion from neurons generated at later times. Similarly, the pyramidal cells of the hippocampus arise from an outward migration of immature neurons from the ventricular zone along radial glia, although the pattern of migration is not as clearly delineated. In contrast, immature neurons originating in the external granule cell layer of the cerebellum migrate predominantly after birth in an inward direction guided by Bergmann glial cells, whereas immature Purkinje cells migrate in the opposite direction from the internal granule layer[7]. Neurons from the ventricular zone migrate to the olfactory bulb *via* neuron-to-neuron connections by chain migration[8].

The characterization of mouse mutants resulting from genetic abnormalities of neuronal migration has provided insight into some of the molecular pathways guiding this process. For example, reeler mice[9–11] or mice with disruption of the genes *Mdab1* (refs 12–14), *Cdk5* (ref. 15) and *Cdk5r* (also known as *p35*; ref. 16), display similar migrational abnormalities. The protein encoded at the reeler locus, reelin, is an extracellular matrix protein secreted by Cajal-Retzius cells[17,18], and the reelin protein may provide an extracellular guidance cue for migrating neurons. Furthermore, reeler mutants, *Mdab1*-deficient, or *Cdk5r*-deficient mice have inversion of cortical layering, and Cdk5r is a brain specific activating subunit of Cdk5 (ref. 19), a neurofilament kinase expressed in postmitotic neurons[20], suggesting that all of these genes disrupt a similar pathway or pathways important for the response of migrating neurons to extracellular signals.

Some human syndromes display cortical dysplasia, and a number of these are postulated to result from abnormal neuronal migration[21]. For example, humans with hemizygous deletions of 17p13.3 have isolated lissencephaly sequence (ILS) or Miller-Dieker syndrome (MDS). These disorders are characterized by type I or classical lissencephaly (agyria/pachygyria), a human brain developmental disorder manifested by smooth brain surfaces and disorganized cortical layering[22]. In addition to lissencephaly, MDS patients have additional dysmorphic features not seen in patients with ILS, which may be the result of different hemizygous deletions.

The gene responsible for type I lissencephaly in ILS and MDS was identified using patient samples with informative deletions of 17p13.3 (ref. 23). This was subsequently confirmed when hemizygous point mutations and an intragenic deletion of a gene termed *LIS1* were found in ILS patients[24]. *LIS1* was found to encode the β subunit of platelet-activating factor acetylhydrolase (PAFAH) isoform Ib[25], an inactivating enzyme for platelet-activating factor (PAF, 1-O-alkyl-2-acetyl-*sn*-glycerol-3-phosphocholine). Consequently, *LIS1* should be referred to as *PAFAH1B1*.

To further understand the function of this gene, and to gain insight into the molecular genetic pathways responsible for neuronal migration, we have produced three different mutant alleles in mouse *Pafah1b1* to examine the consequences of dosage reduction and complete absence of *Pafah1b1* function *in vivo*. The resulting mutant phenotypes are distinct from those of reeler and other mouse mutants, suggesting that *Pafah1b1* participates in a novel pathway for cortical development.

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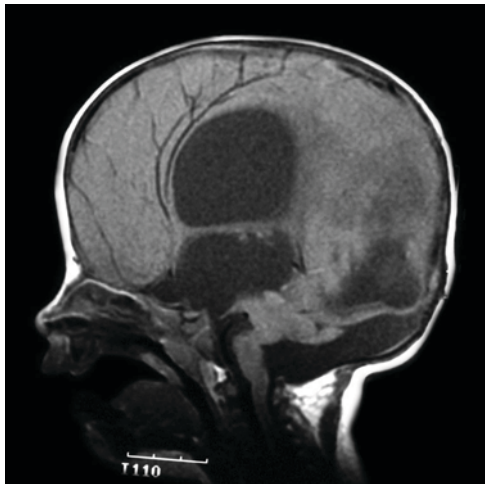
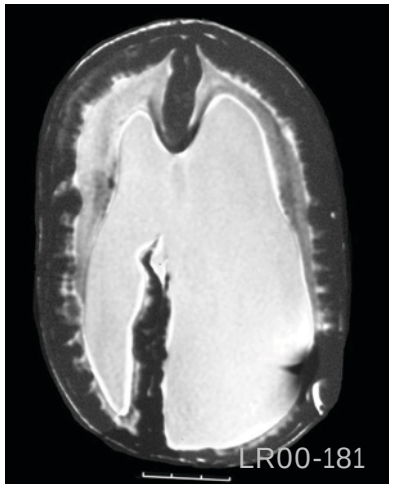
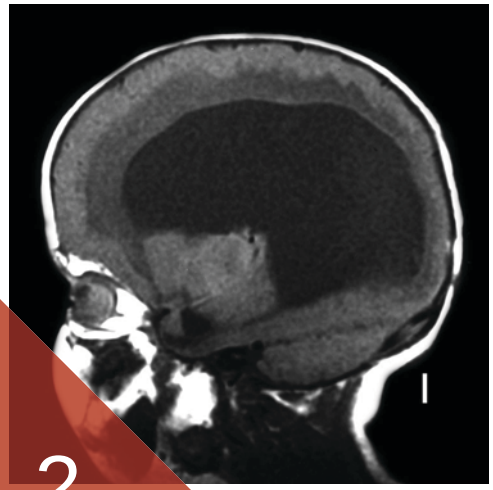
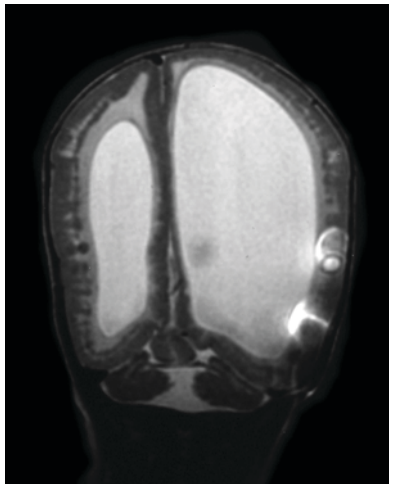
Cobblestone malformation and HYD









Walker-Warburg syndrome
Muscle-eye-brain disease
Fukuyama congenital muscular dystrophy
CMD with mental retardation ++

POMT1$^{-/-}$, *POMT2*$^{-/-}$, *POMGnT1*$^{-/-}$, *FKTN*$^{-/-}$, *FKRP*$^{-/-}$, *LARGE*$^{-/-}$, *ISPD*$^{-/-}$, *LAMC3*$^{-/-}$

This girl has typical, very severe WWS. Note the brainstem kink, very irregular COB cortex, thin beaded subcortical HET, very large LV, and shunt on the L.

1997

American Journal of Medical Genetics 70:67–73 (1997)

Macrocephaly-Cutis Marmorata Telangiectatica Congenita: A Distinct Disorder With Developmental Delay and Connective Tissue Abnormalities

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We describe 13 unrelated children with abnormalities of somatic growth, face, brain, and connective tissue including vasculature. Although the condition in these children falls under the general group of disorders known as cutis marmorata telangiectatica congenita (CMTC), the constellation of abnormalities appears to constitute a distinct and easily recognizable phenotype within this general group. In contrast to most children reported with CMTC, children in this subgroup have a high risk for neurologic abnormalities, including developmental delay, mental retardation, megalencephaly, and hydrocephalus. Early recognition of this condition is important for appropriate surveillance for known complications and parental counseling. Am. J. Med. Genet. 70:67–73, 1997.

KEY WORDS: telangiectasia; congenital overgrowth; hemihypertrophy; megalencephaly

INTRODUCTION

Cutis marmorata telangiectatica congenita (CMTC) is a condition characterized by cutis marmorata, which is congenital generalized or segmental "marbled" or "mottled" skin appearance caused by prominent capillaries and veins, and vascular lesions characterized as telangiectasias, which resemble spider angiomas, and venous dilatation or phlebectasias. Other vascular lesions, such as capillary and cavernous hemangiomas, nevus flammeus, and varicose veins, can also occur [Cohen and Zalar, 1988]. The cause of CMTC is unknown and likely heterogeneous. Way et al. [1974] reviewed 41 cases of CMTC (38 previously published) and found the incidence of associated anomalies to be 50%. More recently, Pehr and Moroz [1993] reviewed 126 affected individuals and reported that 68% had some additional congenital anomaly; however, some were minor or of questionable causal association. The most common associated manifestations included asymmetry, localized limb defects, other vascular anomalies, and glaucoma. Other anomalies such as macrocephaly and developmental delay or mental retardation are low incidence findings in most series [Stephan et al., 1975; Pehr and Moroz, 1993].

In this report we summarize the clinical findings in 13 patients, ages 11 months to 17 years (8 males, 5 females), with a distinct combination of CMTC, abnormal growth patterns, minor craniofacial and skeletal anomalies, central nervous malformation, and abnormal connective tissue and vasculature.

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Macrocephaly with cutis marmorata, haemangioma and syndactyly – a distinctive overgrowth syndrome

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We describe nine children with a similar pattern of features including macrocephaly and cutis marmorata telangiectatica congenita. All were large at birth and had a distinctive capillary haemangioma involving the philtrum and upper lip. The seven who survived all developed hydrocephalus and had developmental delay. Six developed body asymmetry and three had internal arteriovenous malformations. Syndactyly of the second and third toes and/or the third and fourth fingers or toes was commonly seen. All of the cases were sporadic. This condition is easily recognizable and should be considered in the differential diagnosis of patients presenting with overgrowth and macrocephaly.

Keywords: overgrowth, cutis marmorata, macrocephaly, hemihypertrophy

Introduction

The association between macrocephaly, limb asymmetry and angiomatosis was documented in 1975 by Stephan *et al.* They described a heterogeneous group of ten patients with vascular abnormalities including Klippel-Trenauney-Weber syndrome, Sturge-Weber syndrome, and cutis marmorata telangiectatica congenita. All of the patients had unexplained macrocephaly, but intellectual function was normal in seven out of the 10. One of the three mentally retarded patients was large at birth and had a midline haemangioma extending from the forehead to the chin, along with striking and persistent generalized cutis marmorata. She developed ventriculomegaly requiring the insertion of a ventriculo-peritoneal shunt at 5 months of age. She went on to develop hemihypertrophy. At 22 months of age she contracted pneumonia and died. A similar patient was reported by Meyer in 1979. This child, a male, had a large birth weight, macrocephaly, an extensive naevus flammeus of the face and body and right-sided hemihypertrophy. He developed ventriculomegaly which required shunt insertion during the first few months of life and had severe developmental delay. Cristaldi *et al.* (1995) reported two

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Megalencephaly and Perisylvian Polymicrogyria with Postaxial Polydactyly and Hydrocephalus: A Rare Brain Malformation Syndrome Associated with Mental Retardation and Seizures

Abstract

Background and Objective: Megalencephaly (MEG) or enlarged brain occurs as a mild familial variant with normal brain structure, but otherwise is an uncommon human brain malformation that may be associated with significant developmental and neurological problems. It has been classified into anatomic and metabolic subtypes. The clinical findings associated with anatomic megalencephaly have been variable and few distinct subtypes have been described. We report five unrelated children with severe congenital MEG associated with polymicrogyria (PMG), postaxial polydactyly (POLY) and hydrocephalus (HYD).
Methods: The clinical records and brain MRI of five patients have been reviewed.
Results: All patients had striking MEG that was symmetric in three of the five patients, and mildly asymmetric in two. The birth OFC was between +2 and +4 SD. The gyral pattern was irregular with microgyri typical of PMG, which was most severe in the perisylvian region in all five patients. Four of the five had hydrocephalus treated with a shunt. Subsequently, one of the shunted patients had small ventricles while the others had mildly to moderately enlarged lateral ventricles. Three of the five patients had postaxial polydactyly of all four limbs. The corpus callosum was dysmorphic in one patient with a fused rostrum and genu, and intact although mildly thin in the others. None were abnormally thick. All patients had severe mental retardation; three had seizures and another had an epileptiform EEG.
Conclusion: We believe this constellation of findings (MEG-PMG-POLY-HYD) comprises a new and distinct malformation syndrome that we designate the MPPH syndrome.

Key words
Megalencephaly · polymicrogyria · postaxial polydactyly · hydrocephalus · MPPH syndrome

Introduction

Megalencephaly (MEG) or enlarged brain occurs as a mild familial variant with normal brain structure, but otherwise is an uncommon human brain malformation that may be associated with significant developmental and neurological problems. It has been divided into anatomic and metabolic subtypes [5]. The clinical findings associated with anatomic megalencephaly have been variable. Apart from the mild familial type, anatomic megalencephaly has been found in many different disorders including overgrowth syndromes such as Soto [16,20] or Weaver-Smith syndromes [2], and hemangiomatosis-overgrowth syndromes such as Bannayan-Riley-Ruvalcaba [7,13], Cowden [10], and Proteus [3,18] syndromes. MEG also occurs in skeletal dysplasias

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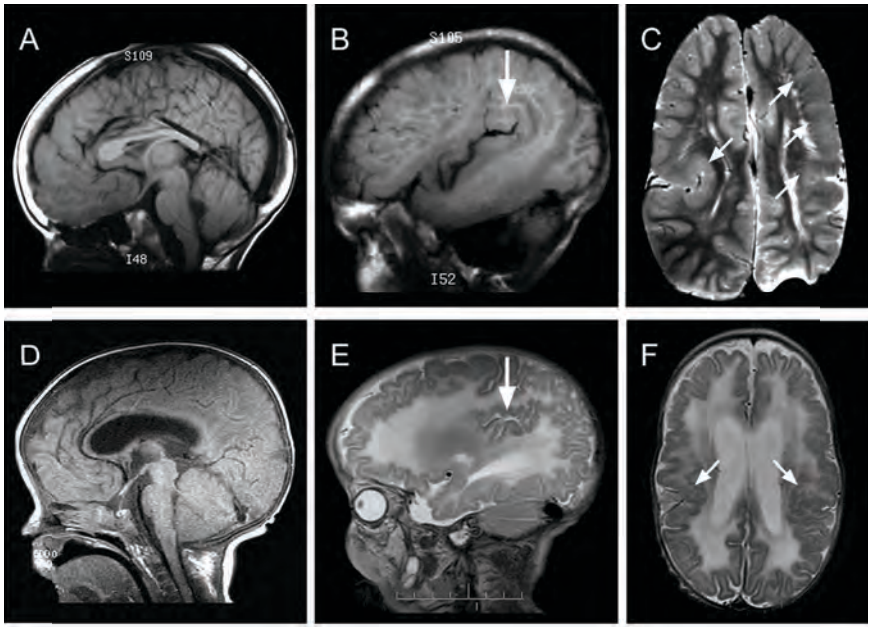

MPPH criteria

- **Constant**
  - Megalencephaly
  - Polymicrogyria
  - DD/MR
- **Frequent**
  - Postaxial polydactyly
  - Hydrocephalus
  - Seizures

MEG and HYD

RAPID COMMUNICATION

AMERICAN JOURNAL OF medical genetics PART A

Megalencephaly-Capillary Malformation (MCAP) and Megalencephaly-Polydactyly-Polymicrogyria-Hydrocephalus (MPPH) Syndromes: Two Closely Related Disorders of Brain Overgrowth and Abnormal Brain and Body Morphogenesis

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- Megalencephaly
  - VMEG in 34/42 (81%)
  - HYD in 17/42 (40%) defined by shunt
- MCAP
  - VMEG 15/21 (71%)
  - HYD 10/21 (48%)
- MPPH
  - VMEG 19/21 (90%)
  - HYD 07/21 (33%)

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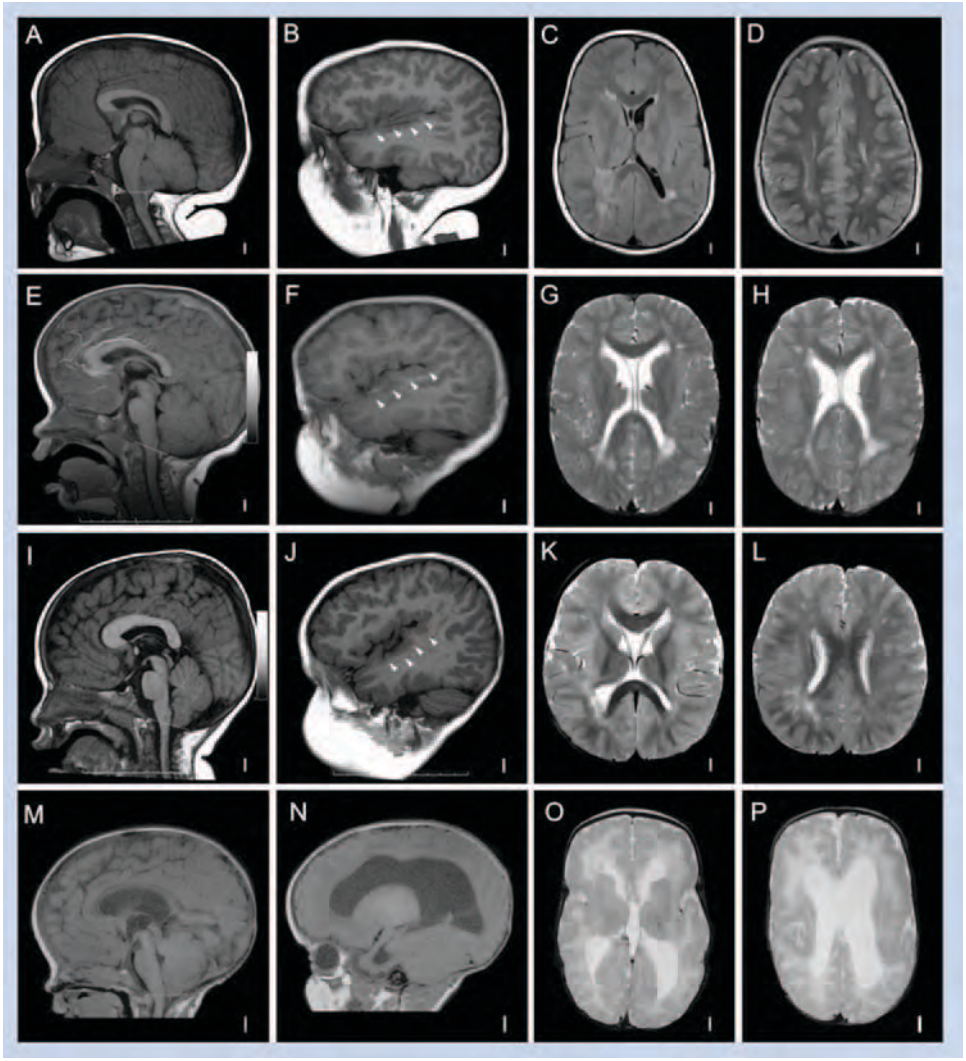
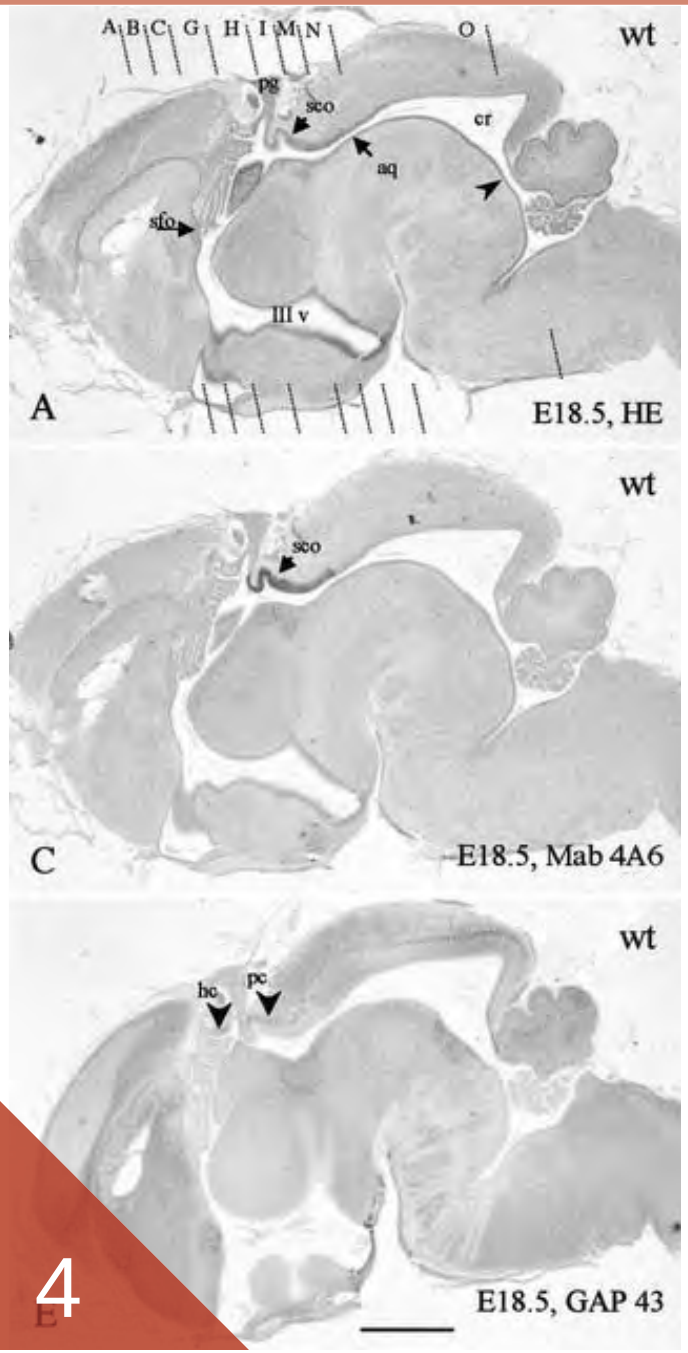
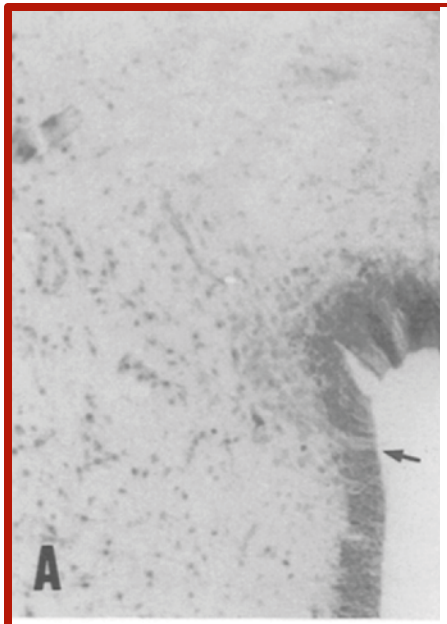


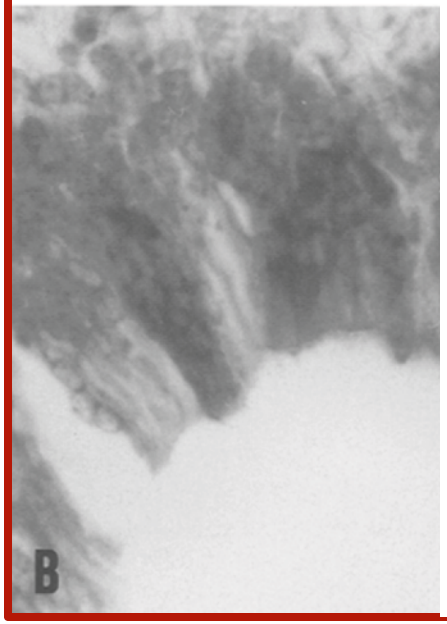


The subcommissural organ

- The posterior commissure (PC) forms in the dorsal midline of prosomere 1
- Beneath the PC, dorsal midline ependyma differentiates into a secretory region: the subcommissural organ
  - Ependyma consists of secretory cells
  - Hypendema consists of glial and parenchymal cells
- The SCO secretes high molecular weight glycoproteins into the 3V at early developmental stages
  - Mouse E14.5 and active for lifetime (most mammals)
  - Human E54 (post-ovulatory) and regresses at puberty
- SCO glycoproteins polymerize into a thick fiber
  - Reissner's fiber
  - This fiber runs along the aqueduct, 4V and spinal central canal but its function in unknown
  - The fiber is never formed in humans
- One SCO secretory glycoprotein (SCO-spondin) has homology to axonal guidance molecules (F-spondin)

SCO in human fetus at 19 wkg





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Developmental Brain Research 79 (1994) 316–320

DEVELOPMENTAL BRAIN RESEARCH

Short Communication

Alterations of the subcommissural organ in the hydrocephalic human fetal brain

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Accepted 10 March 1994

Abstract

We have studied the subcommissural organ of two hydrocephalic brains, of 20 and 21 gestational weeks and of two normal brains, aged 19 and 23 gestational weeks. Both hydrocephalic cases presented a size reduction of the subcommissural organ compared to the normal cases; only in one case, there were also alterations of the morphological components of the subcommissural organ, suggesting different pathogenic relationships between hydrocephalus and dysplasia of the subcommissural organ.

Key words: Subcommissural organ; Hydrocephalus; Human fetal brain

The subcommissural organ (SCO), one of the circumventricular organs [2], lies below the rostral part of the posterior commissure. In the human brain, it appears in the second month of intrauterine life, concurrently with the pineal gland [1], to reach its maximum development during fetal life, regressing around puberty [14]. In the adult, only isolated relicts remain [4].

The SCO is a secretory organ [8]; the secretory material is released into the CSF, where in most species it forms Reissner's fiber (RF). Two main components are distinguished: the secretory cells forming the ependymal part and the hypendyma, which consists of glial, vascular and parenchymal-like cells (for references see [7]); the hypendymal cells have lost the contact with the ventricle [4]. During the fetal period of man, the SCO seems to secrete exclusively CSF-soluble material and does not form RF [8].

The possible relationship between the SCO and hydrocephalus has been observed in experimental animals, such as mutant mice and rats with spontaneously occurring hydrocephalus [11–13] and in rats with induced postnatal hydrocephalus [3]. The findings in the SCO of these animals range from complete absence [12] to a progressive reduction of the organ [3]. The possible association hydrocephalus/alterations of the SCO in the human brain is the subject of the present study.

We examined two hydrocephalic brains, from spontaneous abortions, of 20 and 21 gestational weeks (GW). One of the fetuses (case 1H) presented malformations of the hand, the other (case 2H), was apparently normal. They were compared to two normal brains, aged 19 (case 3N) and 23 GW (case 4N), also from spontaneous abortions. The brains were fixed in Bouin's fluid, embedded in paraffin, cut in the horizontal plane at 10 μm and stained with Cresyl violet. Calculation of the global volume and a 3D-reconstruction of the SCO of the four cases were obtained using an Eutectic SSR-system.

At autopsy, both hydrocephalic brains presented a significant dilatation of the lateral and third ventricles; in case 1H, the Sylvian aqueduct was dilatated, in case

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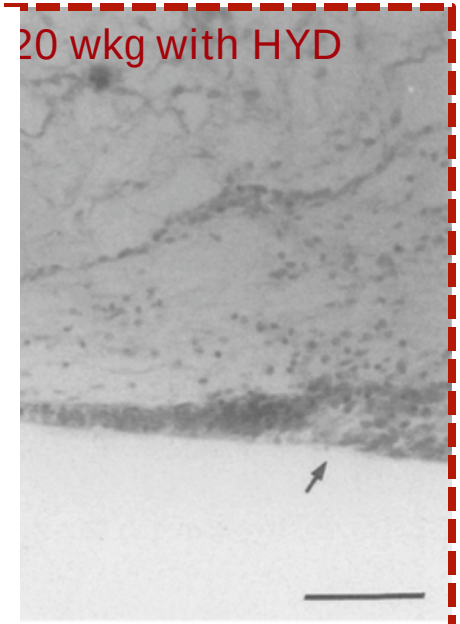
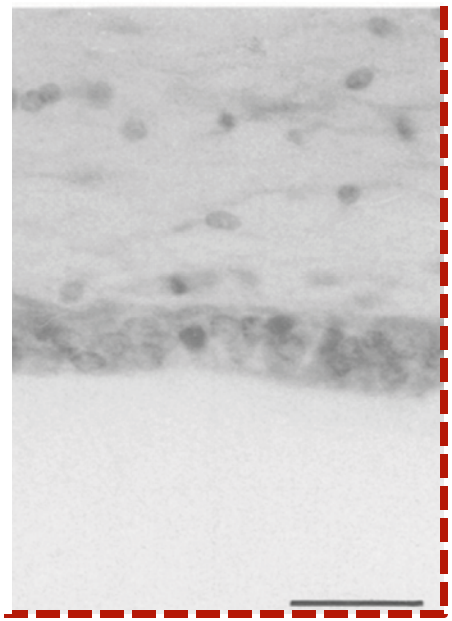
20 wkg with HYD





The SCO and hydrocephalus

Human

- Human disorders with loss of SCO
  - Hydrocephalus, NOS
- Human disorders with loss of SCO
  - *PAX6*$^{-/-}$ possible

Mouse

- Mouse mutants with loss of SCO and HYD
  - *Msi1*$^{-/-}$
  - *Msx1*$^{+/-}$ *and Msx1*$^{-/-}$
  - *Rfx4*$^{+/-}$
  - *Pax6*$^{-/-}$
  - *Wnt1*$^{-/-}$
- Mouse models with HYD caused by teratogens
  - X irradiation
  - Kaolin injection into CM
  - Borna disease virus

Msx1 mouse mutants

$Msx1^{+/-}$

- PC small
- SCO small
  - 1/2 size of normal
- AQ closed
- HYD of 3V-LV in 1/3
- LV wall loss of ependyma seen at P40

$Msx1^{-/-}$

- PC absent in 5/7
- SCO absent in 5/7
  - SCO disrupted in 2/7
- Pineal gland dysplastic
- AQ collapsed in rostral region (7/7)
- HYD of 3V-LV in all mutants

- Msx1 is necessary for development of dorsal midline structures in Prosomere 1

Rfx4 mouse mutants

Rfx4$^{-/-}$

- Condition
  - Perinatal P0 lethal; studied in E12.5 embryos
  - Small head with abnormal dome shape
- Forebrain midline structures
  - Rostral normal or subtle
  - Middle dysplasia with loss of mesial HEM wall, single central LV
  - Caudal severe dysplasia with loss of all dorsal midline structures
    - Pineal gland, PC, SCO
    - Hippocampus

Rfx4$^{+/-}$

- Condition
  - Most survive, large head
  - Severe HYD involving 3V-LV in 75% by 47±3 days
- Forebrain midline structures
  - Pineal gland and PC present and normal
  - Mesial HEM wall intact with two lateral ventricles
  - Caudal mild dysplasia
    - Pineal and PC normal
    - SCO absent

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Developmental Brain Research 152 (2004) 69–72

DEVELOPMENTAL BRAIN RESEARCH

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Short communication

Hemorrhagic hydrocephalus (*hhy*): a novel mutation on mouse chromosome 12

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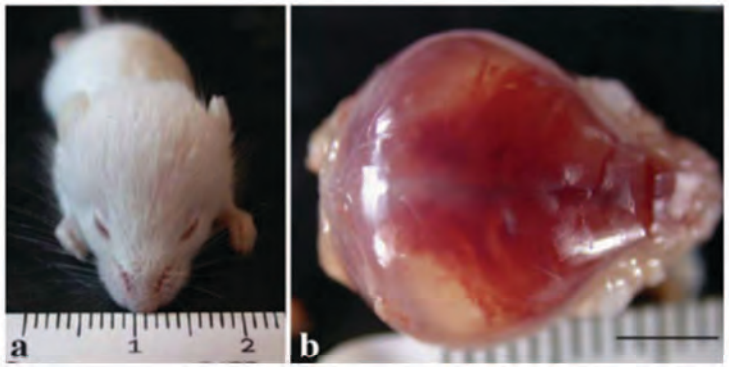
Abstract

A novel mouse hemorrhagic hydrocephalus mutation (*hhy*) inherited in an autosomal recessive manner on chromosome 12 has been found at the Osaka Prefecture University. The *hhy* homozygous mutant had dilated lateral ventricles and a communicating aqueduct, with no histological abnormalities either in the subarachnoid space or in the choroid plexus. Multiple hemorrhages in the meninges and throughout the brain parenchyma of the mutant were relevant to advanced stages of hydrocephalus. Subcortical heterotopia was detected unexceptionally in the mutants. Thus, the *hhy* mutation is characterized by three different abnormalities, i.e. hydrocephalus, intracranial hemorrhage and subcortical heterotopia.

Theme: Development and regeneration
Topic: Developmental genetics

Keywords: Hydrocephalus; Intracranial hemorrhage; Heterotopia; Mouse mutation; Genetic analysis

Hydrocephalus is characterized by an accumulation of cerebrospinal fluid (CSF) in the ventricular system. Patients with hydrocephalus have dilated ventricles due to the pressure of accumulating CSF. Congenital hydrocephalus in humans has been reported to occur with a frequency of 1–3 per 1000 live births. A variety of factors can cause the development of congenital hydrocephalus. In addition to viral infection and developmental anom with hydrocephalus. hydrocephalus inclu tions as well as ge reported. Some of including hydrocep congenital hydrocep cephalic polydactyly cephalus with hop gait (*hyh*) on chromosome 7 exist [1,2,5,7,8]. Both *hy-3* and *ch* develop a communicating type of hydrocephalus resulting from developmental failure of the subarachnoid space. Targeting of *L1*, a neuronal cell adhesion molecule, results in hydrocephalus by abnormal development of ventricular system [3]. The *Msi1* null mutation is associated with obstructive hydrocephalus



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Neurobiology

Ccdc85c Encoding a Protein at Apical Junctions of Radial Glia Is Disrupted in Hemorrhagic Hydrocephalus (*hhy*) Mice

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Masato Ibuki,‡ and Jyoji Yamate†

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Cortical heterotopia, a malformation of the developing cortex, are a major cause of epilepsy and mental retardation in humans. Hemorrhagic hydrocephalus (*hhy*) mutation on mouse chromosome 12 results in subcortical heterotopia and nonobstructive hydrocephalus with frequent brain hemorrhage. Here, we show that coiled-coil domain-containing 85C (*Ccdc85c*), consisting of 6 exons that encode a 420 amino acid protein, is disrupted by replacement of a 3.2-kb sequence, including exon 2 in *Ccdc85c* by a 1.5-kb retrotransposon-like repeat sequence in the *hhy* mutant. Immunoreactivity to Ccdc85C was detected predominantly at the apical junctions of radial glia in the wall of lateral ventricles of the developing brain. In the *hhy* brain at embryonic (E) day 18 (E18), radial glial demise followed by agenesis of the ependymal layer lining the neonatal cortex and accumulation of neuronal specific nuclear protein (NeuN)-positive postmigratory neurons in the subcortical area occurred. Accumulation of E15-born, but not of E13-born, 5-bromo-2′-deoxyuridine labeled neurons expressing special AT-rich sequence binding protein 2 was detected in both heterotopia and the superficial layers of the *hhy* neocortex at postnatal day 7. *Ccdc85c* deficiency permitted radial scattering of paired box gene 6-positive neural progenitors in the ventricular zone, likely resulting in reduced self-renewal of the progenitors in the developing *hhy* cortex. These findings indicate an important role of Ccdc85C in cortical development and provide a mouse model to study pathogenesis of subcortical heterotopia and hydrocephalus. ***(Am J Pathol 2012, 180:314–327; DOI: 10.1016/j.ajpath.2011.09.014)***

Hydrocephalus is a disease characterized by the accumulation of cerebrospinal fluid (CSF) in the brain cavities, resulting in ventricular dilatation. Hydrocephalus is caused by abnormalities in the CSF flow within the ventricular system or production/resorption of CSF by the choroid plexus and subarachnoid space. With or without aqueductal stenosis, hydrocephalus is classified into two types: obstructive hydrocephalus and communicating (nonobstructive) hydrocephalus.

Congenital hydrocephalus is a frequent birth defect in humans, as well as mice. A significant portion of the human cases is genetic in origin, but molecular genetics of this disease is poorly understood.[1] In mice, a number of hydrocephalus mutations have been reported. Some of these hydrocephalus mutations recently identified are implicated in ependymal malfunction, in particular, cilia dysfunction.[2–9] However, molecular mechanisms underlying the development of hydrocephalus remain obscure.

Cortical heterotopia are results of a malformation of the developing cortex. Patients with heterotopia show characteristic disorders such as epilepsy and developmental delay.[10] Heterotopia in humans are classified into two subtypes, nodules of neurons lining the lateral ventricles, namely periventricular heterotopia (PH), and heterotopic neurons arrested under the normal cerebral cortex (ie, subcortical band heterotopia [SBH]). So far, X-linked dominant mutations in the gene for actin-binding phosphoprotein filamin A (*FLNA*) are associated with PH in humans.[11] Human SBH is caused by X-linked dominant

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The genetic basis of hydrocephalus

- Simple inheritance
  - AD, AR and XL disorders
  - Chromosome disorders
- Developmental disorders
  - NTD: myelomeningocele
  - PRO: HPE and ACC ++
  - RHO: DWM, RES, PTCD ++
  - MEG ++
  - HET, LIS, COB, PMG ++
- The CSF system
  - Choroid plexus, ependyma
  - Aqueduct and SCO
  - Ventricles and foramina
  - Extra-axial space

- 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 end?

The genetic basis of hydrocephalus

- Simple inheritance
  - AD, AR and XL disorders
  - Chromosome disorders
- DEV disorders: Neural tube
  - NTD: myelomeningocele
- DEV disorders: Forebrain
  - Holoprosencephaly
    - SHH, ZIC2, ++
  - Agenesis corpus callosum
    - L1CAM, NFIA, NFIB, ++
- DEV disorders: Hindbrain
  - Dandy-Walker malformation
    - FOXC1, ZIC1/4, ++
  - Rhombencephalosynapsis
    - Not identified
- DEV disorders: GROWTH
  - Megalencephaly
    - PTEN, PIK3CA, PIK3R2, AKT3
- DEV disorders: Cortex
  - Neuronal migration (HET)
    - several
  - Neuronal migration (LIS)
    - ARX, LIS1, TUBA1A ++
  - Cortical development
    - POMT1, POMT2, FKTN, ++
- Where do you end?