A NEW FAMILY WITH AUTOSOMAL DOMINANT PORENCEPHALY WITH A NOVEL COL4A1 MUTATION. ARE ARACHNOID CYSTS RELATED TO COL4A1 MUTATIONS?

Summary: A new family with autosomal dominant porencephaly with a novel Col4A1 mutation. Are arachnoid cysts related to COL4A1 mutations?: Porencephaly is an extensively encountered condition in pediatric neurology practice and leads to serious morbidity with its complications. Important etiological factors are trauma, hemorrhage, infection and thrombophilic factors that may cause destruction in the developing brain. Col4A1 mutations were also shown in familial porencephaly cases. We describe two siblings with porencephaly, hemiparesis, epilepsy, atrophic kidney in one of the siblings and asymptomatic mothers with an arachnoid cyst. We performed Col4A1 gene mutation screening and detected a novel mutation in mother and both of the children. This family has some features previously undescribed in patients with mutations of Col4A1 gene like atrophic kidney in one sibling and arachnoid cyst in the mother. We discuss here the possible relationship between these abnormalities and the mutation. Key-words: Porencephaly - Col4A1 - Mutation - Arachnoid Cyst.
A NEW FAMILY WITH AUTOSOMAL DOMINANT PORENCEPHALY WITH A NOVEL COL4A1 MUTATION. ARE ARACHNOID CYSTS RELATED

We present here two siblings with hemiparesis, seizures, and renal atrophy in one of them, found to have porencephaly on brain imaging and mutation analysis showed heterozygote CoUAI mutation, who present in their asymptomatic mother with an arachnoid cyst.

CASES

PATIENT 1

This patient was the second child of unrelated parents. He was delivered by cesarean section at term with a birth weight of 3600 g. Atrophy of the right kidney was detected during routine antenatal follow up. He started unsupported sitting when he was 7 months-old. He was examined at the age of ??-months because of left-sided hemiparesis and motor delay which had noticed at the age of 5-months. At the age of 16 months he could speak a few words during examination. At that age right-sided clonic and secondary-generalized seizures were seen. They were resistant to therapy, and triple antiepileptic therapy had to been started. On cranial magnetic resonance imaging (MRI), a porencephalic cystic cavity was detected at the right side (Fig. 1). Cardiac investigation was normal. Renal ultrasonography (USG) confirmed the diagnosis of atrophic right kidney, and MAG 3 scintigraphy showed that the right kidney has non-functional. As their first child also had similar complaints, MRI studies of the parents were performed and an arachnoid cyst in the left temporo-frontal region was detected in the mother (Fig. 2).

PATIENT 2

Patient 2 was the older sister of patient 1 and she was 5 years-old. She was born at 42 weeks with a birth weight of 3350 gr by cesarean section because of postmaturity.

Although her mental development was compatible with her chronological age, she walked unsupported at second year of her life, possibly due to the operation for a congenital hip dislocation. She had been followed in another center because of her focal and secondary generalized seizures for the last three years. A right hemiparesis was noticed when she was 6-months-old like her brother. Her seizures have been under control by a single antiepileptic drug. On cranial MRI, there was a left-side giant porencephalic cyst extending from the level of the third ventricle and basal ganglia to the vertex, and connected with the ventricular system and 9x7x6 cm in size (Fig. 3). Cardiac and renal investigations were normal.

To investigate the etiology of the porencephalic cyst, prothrombin time (PT), activated partial thromboplastin time (APTT), protein C, protein S activity, antithrombin III quantity, lipoprotein a, homocysteine, vit B12, folic acid, factor VIII, factor IX levels, anticardiolipin and antiphospholipid antibodies, factor V Arg506Gln mutation (factor V Leiden), the C677T and A1298C mutations
of the MTHFR gene and the G20210A mutation of prothrombin gene were investigated in both cases and the parents. Only a homozygote MTHFR A1298C mutation in the mother with heterozygosity in both children was detected.

**PATIENT 3**

She is the mother of both affected children. She was a 30 years old healthy woman. She has no complaints. She was evaluated after both children were diagnosed with familial porencephaly. Neurologic and dysmorphic evaluation was normal while her cranial MRI showed an arachnoid cyst. Her husband was also healthy and cranial MRI studies were within normal limits.

**MATERIALS AND METHODS**

Genomic DNA from the two children and both parents was isolated from peripheral blood using standard procedures.

Genomic DNA was amplified from each exons (52 in total), including at least 50 nucleotides of flanking intronic sequences according to Gould and coworkers (9). Both parents and a panel of 178 control samples of Caucasian origin were screened for the mutation by direct sequence analysis.

**RESULTS**

Genomic DNA sequencing of CoMA 1 from patients 1 and 2 showed a novel heterozygous GGG insertion at nucleotide c. 4814 in exon 51 resulting in an in-frame Gly insertion at position p. 1605 of Col4A1. The same heterozygous mutation was present in the mother but not in the father. A control group of 178 control individuals was evaluated for this novel insertion. None of the 356 control chromosomes carried this variant, suggesting it is non-common in the general population.

Furthermore the in-frame insertion is located in the highly conserved NCl domain and mutations in this domain have been previously described in collagen-related human disease (3, 7). Therefore we considered the C.4816-4818 insertion likely to be pathogenic.

**DISCUSSION**

Porencephaly is a frequent condition in pediatric neurology practice and leads to serious morbidity with complications. Its frequency has been reported as 68% in patients with epilepsy and congenital vascular hemiparesis (4). Important etiological factors are trauma, hemorrhage, infection and thrombophilic factors that may cause destruction in the developing brain. The most commonly implicated condition is the Factor V G 1691 A mutation. A study of 76 porencephaly patients and a control group showed a significantly higher incidence of Factor V G 1691 A mutation and multiple thrombotic risk factors in the patient group (6). In our cases, except for cesarean section due to postmaturity in the older sister and a recurrent cesarean section in the second child, there were no other risk factors such as perinatal hypoxia, premature birth, low birth weight, jaundice, intrauterine infection, hospitalization in the newborn period or trauma. On the other hand, as our both patients were siblings, the most possible gene for this disorder was CoMAl and molecular studies showed a novel mutation in a very conservative region of the gene.

Basal membranes contain collagen type 4, laminin, nidogen, heparin sulphate, proteoglycans and other glycoproteins (17). Unlike most collagene, type 4 collagens are found in the structure of all basal membranes including the vascular basal membrane. It contains six types of collagen chains named and numbered from a 1 (IV) to a6(? V). Collagen IV a2 and a2 chains present in the basal membranes of all tissue types while the other chains distribute more limitedly in other tissue types. For example; a3, a4 and a5 are present in glomeruli, lungs, testes and eyes while a5 and a6 are present in skin, smooth muscle and kidneys. On the other hand, these chains may be expressed in different embryonic developmental stages. For example, in early stages of renal development, a2 and a2 genes are active while a3, a4 and a5 genes are active in later stages. Mutations in genes coding o3, a4 and a5 chains cause Alport syndrome with renal insufficiency and deafness. (12). Recently, the relationship between CoHAl mutations and perinatal cerebral hemorrhagy and familial porencephaly was shown (9). Mutations in this gene cause weakness and fragility of vascular structures. This causes bleeding in small vascular structures, especially in cases of hypertension, trauma, exercise. Col4Al mutations cause a very wide spectrum of clinical pictures as are antenatal cerebral hemorrhagy, porencephaly, infantile hemiparesis. migraine attacks, hematuria, cataract, retinal tortuosity, hemorrhagic strokes in adults or children without porencephaly, periventricular and deep white matter leukoencephalopathy (2, 7, 10, 19, 20). On the other hand, Col4Al mutations
cause a newly described syndrome, HANAC syndrome, clinical features with hereditary angiopathy, nephropathy, aneurysms and muscle cramps as clinical features (14). The cause of this wide clinical spectrum is most likely to be related with the presence of Col4Al in all basal membranes (12). In the present siblings, hemiparesis was detected nearly at the 6th month after birth, with epileptic attacks, and renal atrophy in addition to porencephaly in the little brother. The relationship between Col4A 1 and renal problems has been shown in previous animal studies (9). However, there is no report on human renal problems related with this gene except the renal cyst in HANAC syndrome and hematuria. As Col4A 1 is also expressed in renal tissue, this prenatally diagnosed renal atrophy/ hypotrophy may be related with this mutation (12).

As mutations of this gene are not fully penetrant, some persons with these mutations may be asymptomatic. On the other hand, clinical expression presents variability within the same family members. In our family, the children have porencephaly while the only feature of the mother is an arachnoid cyst detected during family screening.

Arachnoid cysts are cavities lined with collagen and arachnoid cells and are located within the arachnoid membrane and do not communicate with the ventricular system (18). There is no clear explanation for the development of arachnoid cyst but the main theory is abnormal mesenchymal condensation and cerebrospinal fluid flow. As they associate some developmental abnormalities of the brain like heterotopias, it seems like a developmental abnormality. In some studies, the main abnormality described abnormal trabeculation and presence of tightly packed collagen fibrils instead of trabeculy in the cyst structure (8).

As there is no other case with Col4Al mutation and arachnoid cyst, it is hard to prove the relationship. However, some of the arachnoid cysts are familial and sometimes it may be associated with polycystic kidney and some types of muscular dystrophy (1). Mutations of the collagen genes and other basal membrane proteins may play a role in arachnoid cyst development.

In summary, we present here a family with a Col4Al mutation related porencephaly and their previously undescribed features, renal atrophy and asymptomatic arachnoid cyst and discuss the possible etiological relationships. Further studies are needed to prove the etiological relation of CoHAl mutations with renal atrophy and arachnoid cysts.

References:


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