

Familial porencephaly

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[Abstract](#)

[Key words](#)

[Disease name](#)

[Definition](#)

[Excluded diseases](#)

[Epidemiology](#)

[Clinical description](#)

[Diagnostic methods](#)

[Etiology](#)

[Genetic counseling](#)

[Antenatal diagnosis](#)

[Management including treatment](#)

[Prognosis](#)

[References](#)

Abstract

Porencephaly is a circumscribed intracerebral cavity of variable size which may be bordered by abnormal polymicrogyric grey matter. In extreme cases, this cavity may result in a communication between the pial surface and the ventricle; this is termed schizencephaly. The disease typically manifests in infants. The clinical manifestations of porencephaly depend on the location and the size of the lesion. Hemiplegic cerebral palsy is the commonest feature. Mental retardation and epilepsy are frequently found. According to their topography, which usually corresponds to territories supplied by cerebral arteries, porencephaly (like schizencephaly and polymicrogyria) is thought to result from an ischemic injury, occurring at mid-gestation. Most cases are sporadic. However, some observations of familial recurrences have been reported, suggesting that genetic factors could be involved. Search for mutations leading to a hypercoagulable state is under investigation. Recently, mutations in the COL4A1 gene have been described in four of the already published families with porencephaly and in one new unrelated family. Familial porencephaly is a very rare condition usually transmitted as an autosomal dominant trait with incomplete penetrance. There is no specific treatment. Symptomatic treatment includes physical therapy, anti-epileptic drugs if epilepsy, and shunting procedures for treatment of hydrocephaly.

Key words

Familial porencephaly, schizencephaly, cerebral palsy, stroke, polymicrogyria, autosomal dominant

Disease name

Familial porencephaly

Definition

Porencephaly is a circumscribed intracerebral cavity of variable size which may be bordered by abnormal polymicrogyric grey matter [1].

Excluded diseases

Sporadic porencephaly, schizencephaly

Epidemiology

Porencephaly seems extremely rare [2].

Clinical description

Porencephaly is a term which describes a cerebral image (cysts or cavities in the brain). The disorder occurs before birth. Most infants show symptoms of the disorder shortly after birth and the diagnosis is usually made before one year of age. The clinical symptoms are variable and depend on the location and size of the lesion. Some patients may develop only minor neurological problems and have normal intelligence while others may be severely disabled [2]. The commonest features are hemiplegic cerebral palsy, mental retardation and epilepsy. Other features encountered are: delayed growth, hypotonia, macrocephaly or microcephaly. Patients with porencephaly may have poor or absent speech development, hydrocephaly and limb spasticity.

Diagnostic methods

- Neuroimaging: computerized tomography (CT) and cerebral magnetic resonance imaging (MRI)
- Positive familial history

Etiology

According to their topography (which usually corresponds to territories supplied by cerebral arteries) porencephaly, like schizencephaly and polymicrogyria, is thought to result from an ischemic injury, occurring at mid-gestation [3-4]. Most cases are sporadic and various risk factors have been identified: toxemia, maternal injuries, maternal infection, maternal diabetes, gemellarity, maternal intake of alcohol or cocaine, allo-immune thrombopenia, perinatal asphyxia [5].

However, some observations of familial recurrences have been reported, suggesting that genetic factors could be involved [6-21]. The inheritance follows an autosomal dominant pattern with reduced penetrance. Genes involved in familial porencephaly have not yet been mapped. A first approach could be the search of mutations leading to a hypercoagulable state. Indeed, activated protein C (APC) resistance has been identified as a cause of hemiplegic cerebral palsy in children heterozygous for factor V Leiden mutation [22]. The possible role of

deficiencies in the protein C anticoagulant pathway in the pathogenesis of porencephaly was confirmed in a more recent study [23]. Currently, the National Institute of Neurological Disorders and Stroke (NINDS) conducts a pilot study on abnormal acquired and genetic coagulation factors in children with porencephaly and stroke. In the family reported by Vilain *et al.* [20], all tested affected members of the family were heterozygous for a mutation, which has been considered responsible for increased risk of thrombophilia either at a homozygous state or in combination with heterozygosity for another mutation [20]. In this family, only one of four affected patients tested had the R506Q mutation in factor V Leiden and none of three affected patients tested had a deficiency in protein C. Two of these patients were heterozygous for G20210A *prothrombin* gene mutation, one being also heterozygote for the C677T mutation in the *methylene tetrahydrofolate reductase (MTHFR)* gene. Another patient was only heterozygote for the C677T *MTHFR* gene mutation. Considering the fact that the G20210A *prothrombin* gene mutation leads to hyperprothrombinemia [24], these data suggest that this mutation could play a role in the pathogenesis of porencephaly but is clearly not the only pathogenic factor. Similar conclusions emerged from studies designed to evaluate the risk of venous thrombosis in heterozygous carriers of the 20210A allele [25-26]: it was concluded that the risk of deep venous thrombosis and cerebral venous thrombosis was increased only in patients who were heterozygous for both factor V Leiden and *prothrombin* gene mutations. Another study reported asymptomatic relatives of heterozygous carriers of the 20210A variant with a history of thromboembolism who were homozygous for this variant [27]. The pathogenic role of the C677T *MTHFR* gene mutation is very unlikely as the relationship between homozygosity for this mutation and venous thrombosis remains controversial [24]. However, increased frequency of combined *MTHFR* C677T and A1298C mutated alleles in spontaneous aborted embryos have been reported [28].

Vilain *et al.* have proposed that, in their family, there is a not yet identified mutation that would cause porencephaly in combination with a heterozygous state for a mutation involved in thrombophilia [20]. This hypothesis would explain the autosomal dominant transmission and the low penetrance of the disorder. The candidate genes are homeobox genes. This is supported by the finding of mutations in the homeobox gene *EMX2*, not only in sporadic cases of schizencephaly [29], but also in two siblings with schizencephaly [17].

Mancini *et al.* [21] reported the presence of patchy hyperintense white matter lesions on T2 MRI of patients and an asymptomatic obligate carrier, and suggested that these lesions could be a marker for the disease. However the specific value of these MRI lesions seems very doubtful. Indeed, periventricular hyperintense white matter lesions of variable size and extent are found in about 50 % of normal controls aged 21 to 59 years [30] and in nearly all normal controls above the age of 60 years [31].

Recently, mutations in the *COL4A1* gene have been described in four of the already published families and in one new unrelated family [32-34]. Electromicroscopy of the skin biopsy can be helpful to rule out patients with *COL4A1* gene mutations before asking for the molecular genetic diagnosis [34].

These mutations result in an abnormal vascular basal membrane. Breedveld *et al.* [33] suggest that trauma and thrombophilia could represent factors influencing the occurrence of cerebral bleeding in carriers of a mutation in the *COL4A1* gene.

Genetic counseling

In the absence of a positive family history and increased risk factors for a hypercoagulable state, the recurrence risk of porencephaly is very low as familial porencephaly is extremely rare.

In case of positive family history, the mode of inheritance is autosomal dominant with reduced penetrance.

Antenatal diagnosis

Some cases may be diagnosed during pregnancy by fetal ultrasonography or MRI, usually in the third trimester.

Management including treatment

There is no specific treatment for this disorder. Symptomatic treatment includes physical therapy, medication for seizures (anti-epileptic drugs), and shunting procedures for treatment of hydrocephaly.

Prognosis

The prognosis for children with porencephaly varies according to the location and extent of the cysts or cavities. Some children develop only minor neurological problems and have normal intelligence, while others may be severely disabled and may die before reaching adulthood.

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