

Familial Porencephaly

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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 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. Genes involved in familial porencephaly have not yet been mapped. A first approach could be the search of mutations leading to a hypercoagulable state. 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 if hydrocephaly.

Keywords

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 (Friede, 1989).

Excluded diseases

Sporadic porencephaly, schizencephaly

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 (Barth, 1987; Barkovich *et al.*, 1992). Most cases are sporadic and various increased risk factors have been identified: toxemia, maternal injuries, maternal infection, maternal diabetes, gemellarity, maternal intake of alcohol or cocaine,

allo-immune thrombopenia, perinatal asphyxia (Boulier *et al.*, 2003).

However, some observations of familial recurrences have been reported, suggesting that genetic factors could be involved (Berg *et al.*, 1983; Airaksinen, 1984; Smit *et al.*, 1984; Zonana *et al.*, 1986; Sensi *et al.*, 1990; Robinson, 1991; Hilburger *et al.*, 1993; al-Shahwan and Singh, 1995; Haverkamp *et al.*, 1995; Andermann and Andermann, 1996; Bonnemann and Meinecke, 1996; Granata *et al.*, 1997; Van Bogaert *et al.*, 1998; Guerreiro *et al.*, 2000; Vilain *et al.*, 2002). 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 incriminated as a cause of hemiplegic cerebral palsy in children heterozygous for factor V Leiden mutation (Thorarensen *et al.*, 1997). The possible role of deficiencies in the protein C anticoagulant pathway in the pathogenesis of porencephaly was confirmed in a more recent study (Debus *et al.*, 1998). Currently the National Institute of Neurological Disorders and Stroke (NINDS) supports a pilot study of abnormal acquired and genetic coagulation factors in children with porencephaly and stroke. In the family reported by Vilain *et al.* (2002), 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 (Vilain *et al.*, 2002). 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 (Seligsohn and Lubetsky, 2001), 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 (Martinelli *et al.*, 1998; De Stefano *et al.*, 1999): 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 (Souto *et al.*, 1999). The pathogenic role of the C677T *MTHFR* gene mutation is very unlikely as the relationship between homozygosity for this mutation and venous thrombosis remains also controversial (Seligsohn and Lubetsky, 2001). However increased frequency of combined *MTHFR* C677T and A1298C mutated alleles in spontaneous aborted embryos have been reported (Zetterberg *et al.*, 2002).

Vilain *et al.* (2002) 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. This hypothesis would explain the autosomal dominant transmission and the low penetrance of the disorder. 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 (Brunelli *et al.*, 1996), but also in two siblings with schizencephaly (Granata *et al.*, 1997).

Clinical description

Porencephaly is a term which describes a cerebral image. 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 (NINDS). 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

Epidemiology

Porencephaly seems extremely rare (NINDS).

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 foetal ultrasonography or MRI, usually in the third trimester.

Management including treatment

There is no specific treatment. Symptomatic treatment includes physical therapy, anti-epileptic drugs if epilepsy, and shunting procedures if hydrocephaly.

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