The Factor V G1691A Mutation Is a Risk for Porencephaly: A Case–Control Study

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This study was initiated to investigate prothrombotic risk factors in children with porencephaly. 76 porencephalic and 76 healthy infants were investigated for factor V (FV) G1691A mutation, factor II G20210A variant, methylenetetrahydrofolate reductase (MTHFR) C677T genotype, lipoprotein (a), protein C, protein S, and antithrombin. Only the FV mutation ($p = 0.005$) and combinations of two or three different risk factors ($p = 0.003$) were significantly associated with porencephaly. These data give evidence that the FV G1691A mutation and a combination of prothromboic factors play a major role in the development of childhood porencephaly.

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The term *porencephaly* commonly refers to cavitating lesions filled with fluid or cerebrospinal fluid in the cerebral parenchyma. Causatively, multicystic encephalomalacia, schizencephaly, and hydranencephaly have been assigned to porencephaly as extreme forms.[1] Little is known of the prevalence of porencephaly, but it has been reported in up to 6.8% of patients with cerebral palsy born at term[2] or in 68% of patients with epilepsy and congenital vascular hemiparesis.[3] Among developmental malformations, direct damage as mechanical trauma, inflammation,[4] or hemorrhage might account for cystic brain lesions. Some familial cases of porencephaly are on record, but a definite origin could not be detected in those cases.[5] The territorial distribution of most porencephalic lesions, however, strongly supports thromboembolic events. In the absence of postnatal strokes, a prenatal origin has to be considered.[6] If thromboembolic events are responsible for destructive processes leading to porencephaly, congenital or acquired states of hypercoagulability might be detected long after the insult took place. In a previous series of 24 children, markers of thrombophilia were found in a considerable number of patients.[7] In that study, a protein C deficiency type I was predominant (6 of 24 patients). Thorarensen and colleauges proposed an association between hemiplegic cerebral palsy including porencephaly caused by the factor V (FV) G1691A mutation.[8]

This study was initiated to investigate genetic factors of thrombophilia in a larger group of patients in comparison with a control group matched for age and ethnic origin on statistical grounds.

Subjects and Methods

Ethics

This study was performed in accordance with the ethical standards laid down in the updated relevant version of the Declaration of Helsinki and approved by the medical ethics committee at the Westfälische Wilhelms-University, Münster, Germany.

Inclusion Criteria

Patients from different geographic areas of Germany diagnosed with porencephaly during infancy by neuroimaging (computed tomography [CT] or magnetic resonance imaging [MRI] scans) but without clinical evidence of postnatal stroke were included.

Exclusion Criteria

Patients with multicystic encephalomalacia, schizencephaly, or hydranencephaly were not considered for inclusion, because we believe that these rare and more extensive lesions might rather result from global hypoxic events or misguided cerebral development.

Control Group

Patients were matched with healthy white infants from the same geographic regions.[9] Controls were recruited between January 1996 and June 2003. They comprised infants with no history of chronic disease or of thromboembolic events and without any medication at the time of recruitment, who presented as outpatients for evaluation before minor surgery (planned circumcisions and hernias) or bone marrow donation.

Laboratory Tests

With parental consent, the FV G1691A and factor II (FII) G20210A mutations, methylenetetrahydrofolate reductase C677T genotype, resistance to activated protein C, concentration of lipoprotein (Lp) (a), protein C (PC), protein S (PS), and antithrombin (AT) were investigated in patients and controls using standard laboratory techniques.[10] A type I deficiency (AT, PC) was diagnosed when functional plasma activity and immunologic antigen concentrations of a protein

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were repeatedly shown to be below 50% of the normal age-related limit.[11] A type II deficiency (AT, PC) was diagnosed in patients with repeatedly low functional activity along with normal antigen concentrations. The diagnosis of PS deficiency was based on reduced free PS antigen levels combined with decreased or normal total PS antigen concentrations, respectively. Serum levels of Lp(a) greater than 30mg/dl were considered elevated, and 28 kringle IV was used as the cutoff for the definition of small Apo(a) isoforms. Criteria for the hereditary nature of a hemostatic defect were present in at least one first-degree family member, or the identification of a causative gene mutation, or both.

Statistical Analysis

All statistical analyses were performed with the StatView 5 software package (SAS Institute, Cary, NC) and the MedCalc software package (MedCalc, Mariakerke, Belgium). To compare the rate of prothrombotic risk factors between patients and controls, to evaluate an independent contribution of thrombophilia to the occurrence of porencephaly, and to adjust the potential cofounders, we estimated the odds ratios (ORs) together with 95% confidence intervals (CIs) by multivariate analysis using a conditional logistic regression model. In addition, prevalences of prothrombotic risk factors in patients and control subjects were calculated by χ^2-analysis or, where relevant, Fisher's exact test. The significance level was set at 0.05.

Results

Seventy-six white patients with porencephaly diagnosed during infancy were enrolled in the study; 76 healthy children were recruited for the control group. Each group comprised 37 males and 39 females. The age of the patients and of the control group subjects at the time of blood testing ranged from 8 months to 23 years. Forty-six percent of the patients with porencephaly presented with focal or secondary generalized seizures, 19% with spastic hemiparesis, and 16% with a combination of the two.

Distribution of Prothrombotic Risk Factors

At least one established prothrombotic risk factor was found in 40 of the 76 patients (52.6%) but in only 24 of the control infants (31.6%; OR, 2.4; 95% CI, 1.2–4.7; $p = 0.015$). The distribution of prothrombotic risk factors in patients is shown in the Table. Multivariate analysis showed significantly higher prevalences of the FV G1691A mutation in the patient group, including 18 patients carrying the heterozygous and 1 infant carrying the homozygous AA genotype. No significant differences were found for frequencies of FII G20210A, elevated Lp(a), protein C deficiency, or antithrombin deficiency. Protein S deficiency was not diagnosed in the patient or in the control population.

Combinations of prothrombotic defects were not found in the control group. However, eight double thrombophilic defects and one triple were diagnosed in the patient group, not including one child with the homozygous FV G1691A mutation. This finding of multiple prothrombotic risk factors in the porencephaly group is highly significant ($p = 0.003$, Fisher's exact test).

Both groups (patients and controls) were matched for premature birth (n = 14) and birth asphyxia (n = 3). Two mothers in the patient group were suffering from hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. These perinatal problems and smoking as a risk factor for thrombembolism were equally distributed in both groups, but an additional risk from the combination of the above mentioned risks and the prevalence of thrombophilic markers could not be confirmed.

Discussion

Periventricular hypoxic lesions in cerebral palsy might represent one end of the spectrum of ischemic events

Table. Multivariate Analysis of Thrombophilic Markers in 76 Children with Porencephaly and 76 Healthy Individuals

Marker	Patients		Controls	OR	95% CI	*p*
FV G1691A	Single defect	14	4	5.8	1.7–20.1	0.005
	Combined defect	5	—			
Lipoprotein (a) (>30mg/dl)	Single defect	5	6	2.1	0.6–7.1	0.2
	Combined defect	5	—			
MTHFR C677T	Single defect	5	10	0.6	0.2–2.4	0.5
	Combined defect	4	—			
F II G20210A	Single defect	2	2	2.3	0.3–17.2	0.4
	Combined defect	2	—			
PC deficiency	Single defect	2	—	—	—	0.2
	Combined defect	1	—			
AT deficiency	Single defect	1	—	—	—	—
PS deficiency	—	—	—	—	—	—

The specific combinations of these markers were FV G1691A + Lp(a) (n = 2), FV G1691A + MTHFR C677T (n = 2), Lp(a) + MTHFR C677T (n = 1), Lp(a) + FII (n = 1), FII G20210A + PC deficiency (n = 1), FV G1691A + Lp(a) + MTHFR C677T (n = 1).

OR = odds ratio; CI = confidence interval; FV = Factor V; MTHFR = methylenetetrahydrofolate reductase; F II = Factor II; Lp (a) = Lipoprotein (a); PC = protein C; PC = protein C; AT = antithrombin.

during pregnancy and porencephaly the other. In a series of three cases, Thorarensen and colleagues proposed an association between hemiplegic cerebral palsy caused by different intracerebral pathologies and the FV G1691A mutation,[8] which leads to resistance to activated protein C, first described by Dahlbäck and colleagues in 1993.[12] Among others, the FV G1691A mutation has been established as a risk factor for cerebral thromboembolism in neonates, infants, and children.[13]

To our knowledge, this is the first case–control study analyzing thrombophilic risk factors in childhood porencephaly. The results show a significantly higher prevalence of the FV G1691A in the patient group. The assumption that childhood porencephaly might be caused by hypercoagulable states is confirmed by these data. However, other single prothrombotic factors such as protein C deficiency, which has been assigned to porencephaly,[7] or elevated lipoprotein (a), which has been found to play a role in stroke in white neonates,[9] did not reach statistical significance in this study.

In the former report, methods and definitions of protein C deficiency did not differ from those in this study. The fact that a different population from a limited geographic area was investigated might be responsible for the difference in the results.

Exogenous risk factors or triggering events leading to neonatal strokes, for example, asphyxia, infections, meningitis, drugs, etc.[9,14] are likely to encourage fetal thrombus formation as well. Because pregnant women are in an acquired hypercoagulable state,[15] the fetus also might be at risk for the same reasons. The FV G1691A mutation in mothers was found to be associated with recurrent fetal loss[16] and preeclampsia.[17] It is known that genetic prothrombotic risk factors lead to placental thrombosis in the fetal and maternal circulation.[18] Also, other acquired and temporary maternal hypercoagulable states may considerably enhance the thromboembolic risk to the fetus and its brain. For hyperhomocysteinemia and antiphospholipid antibodies, an association with fetal loss and preeclampsia has been reported.[19,20]

In our series, no familial cases of porencephaly have been observed. The high prevalence of combined genetic prothrombotic risk factors in the porencephaly group but not in the control group indicates a multifactorial process resulting in thrombembolic events leading to porencephaly. Exogenous factors during pregnancy also may contribute to critical hypercoagulable states. A different pathogenesis may be responsible for some published familial cases of porencephaly with additional somatic anomalies.[5]

Developmental genetic disorders may lead to intraparenchymal cavitations too.[23] The FV G1691A mutation or other risk factors of thrombophilia might pave the way in these cases, but the FV G1691A mutation has not been found consistently in the familial cases.

Whether further prothrombotic risk factors are associated with this pathophysiology still remains an open question. Despite ORs above 2.0 for lipoprotein (a), factor II G20210A, and anticardiolipin antibodies, the results of this study did not reach statistical significance. Further international multicenter studies could help specify the risk factors and their combinations through increased statistical power. However, different ethnic backgrounds applying to the prevalences of the genetically determined risk factors have to be taken into account. Also, prenatal and perinatal exogenous risks should be analyzed in more detail. This will be crucial for any preventive measure.

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Bilateral Globus Pallidus Stimulation for Huntington's Disease

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Bilateral globus pallidus internus (GPi) deep brain stimulation (DBS) was performed in a patient with Huntington's disease (HD) with severe chorea. Stimulation at 40 and 130Hz improved chorea. Stimulation at 130Hz slightly worsened bradykinesia overall, whereas 40Hz had little effect. A [^{15}O] H_2O positron emission tomography showed increased regional cerebral blood flow in motor decision making and execution areas more evident at 40Hz. Adjustment of stimulation parameters in GPi DBS may have the potential to optimize the motor response in HD, improving chorea without aggravating bradykinesia.

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Huntington's disease (HD) is a fatal autosomal dominant neurodegenerative disorder, characterized by progressive cognitive impairment, movement disorders, and psychiatric symptoms. When the movement disorder, particularly the chorea, is disabling, the standard treatment is pharmacological. However, clinical efficacy varies and adverse events are commonly dose limiting. Bilateral pallidotomy was performed in one patient with the Westphal variant of HD but was found to be largely ineffective.[1] In addition, bilateral human fetal striatal transplantation has shown variable clinical results.[2,3] Because of the striking effects of pallidal surgery for choreodystonic movements induced by L-dopa in Parkinson's disease (PD),[4,5] we decided to perform bilateral globus pallidus (GP) deep brain stimulation (DBS) in a patient with severe chorea due to HD. We report these results along with a brain positron emission tomography (PET) study performed after surgery

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