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Recurrent transient ischemic attacks in a 15-year-old boy with β-thalassemia minor and thrombophilia
Contribution of perfusion SPECT to clinical diagnosis

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Abstract

β-Thalassemic patients exhibit an increased frequency of thrombotic events but most patients with heterozygous β-thalassemia minor are asymptomatic and no single case with β-thalassemia minor and concurrent stroke was reported. We present a 15-year-old boy with heterozygous β-thalassemia minor who developed recurrent transient ischemic attacks as documented with repeated brain SPECTs whereas structural neuro-imaging was not contributory. The patient exhibited resistance to activated protein C due to heterozygosity for factor V Leiden as well as slightly decreased plasma levels of protein C and S. This unique association of risk factors might have caused clinically significant thrombophilia resulting in recurrent cerebrovascular events.

This case report underlines the thrombogenic risk of heterozygous β-thalassemia minor in children heterozygous for factor V Leiden mutation. We therefore suggest to screen for thrombophilia in children with β-thalassemia minor when thromboembolism-related phenomena occur. This case also demonstrates that brain perfusion SPECT is a useful and sensitive tool for detecting cerebrovascular events in patients with hemoglobinopathies.

Key words : Stroke ; transient ischemic attack ; SPECT ; thalassemia ; thrombophilia.

Introduction

It is well known that β-thalassemic patients exhibit an increased frequency of thrombotic events but patients with heterozygous β-thalassemia minor are usually asymptomatic. Review of available literature only displays a few patients with β-thalassemia intermedia (a moderate presentation of homozygous thalassemia) and concurrent stroke but no single case with β-thalassemia minor and stroke. Giordano *et al.* (1997) described a 10-year-old patient with β-thalassemia intermedia who developed a left temporo-parietal stroke. Screening for resistance to activated protein C (APC-r) was positive and molecular diagnostic testing revealed heterozygosity for factor V Leiden. Retrospectively studying the number of thrombotic events in a group of 85 homozygous β-thalassemic patients, only one thrombotic event was observed as a case of stroke in a patient with β-thalassemia intermedia with APC-r and a pronounced hematocrit increase (Giordano *et al.*, 1998).

Factor V Leiden, the genetic defect underlying APC-r, and deficiencies of coagulation inhibitors such as antithrombin III, protein C and protein S are known risk factors for venous thrombosis but their role for arterial vascular events and in particular cerebrovascular disease remains controversial (Ridker *et al.*, 1995 ; Albucher *et al.*, 1996 ; Roosendaal *et al.*, 1997 ; Lalouschek and Mannhalter, 1998). There is however evidence that factor V Leiden is a risk factor for childhood stroke (Becker *et al.*, 1998 ; Kenet *et al.*, 2000).

Case report

A 15-year-old right-handed nonsmoking boy of Spanish origin was admitted because of sudden onset of aphasia and a right homonymous hemianopia. The symptoms completely vanished within 60 minutes. Two months before the current admission, two similar episodes had presented. No headaches or other neurological symptoms were observed during or following these episodes.

The patient and his father were known to have heterozygous β-thalassemia minor. The patient's father (aged 50 years) was asymptomatic. Both parents of the patient's mother suffered from recurrent strokes presenting at age ranging from 65-75 years. The medical history of the patient's mother was not contributory.

The clinical neurological examination at admission revealed a Broca's aphasia and a right homonymous hemianopia. Within 60 minutes after onset, the clinical neurological examination had completely normalized. Except for a grade 2/6 systolic murmur at the second right intercostal space, the general physical examination was normal.

A brain Computerized Tomography (CT) performed on the day of admission revealed a small

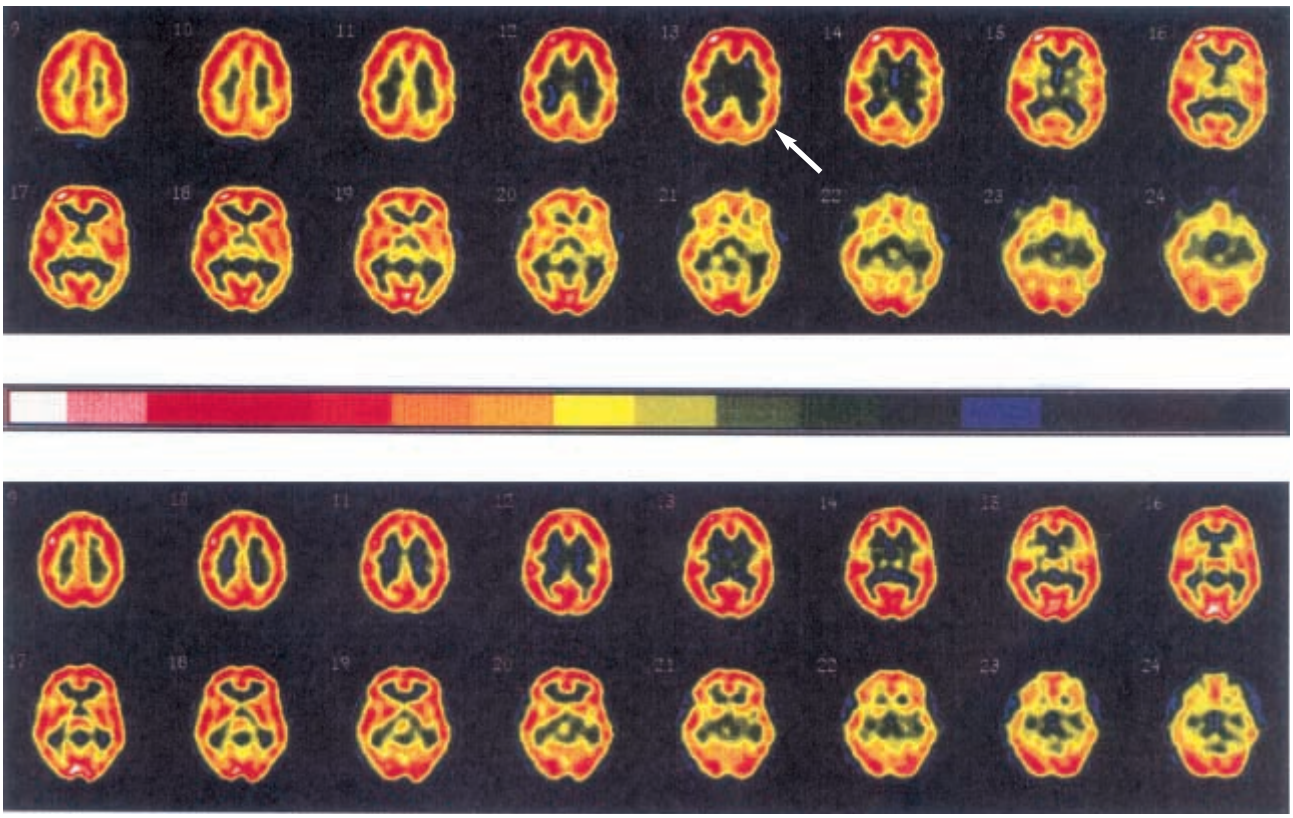

FIG. 1. — Acute phase brain SPECT showed a relative hypoperfusion in the territories of the left middle and posterior cerebral arteries (upper panel, arrow), which significantly improved as demonstrated by repeated SPECT 18 months later (lower panel).

hypodensity in the left temporal region. Brain Magnetic Resonance Imaging (MRI) revealed a small arachnoid cyst in the left temporal region. Standard electroencephalogram and transthoracic echocardiography were normal.

Forty min after onset of symptomatology, 740 MBq of Tc-99m-ethylenecysteine dimer (ECD) was administered intravenously. Brain Single Photon Emission Computed Tomography (SPECT) acquisitions were started 20 min after radiopharmaceutical injection, using a three-detector system (Triad 88, Trionix Research Laboratory, USA) equipped with high-resolution fan-beam collimators. Data were collected for 120 projections (15 seconds per projection, 128x128 matrix, pixel size 36 mm) over 360 degrees, resulting in 45 seconds per projection. A Butterworth filter (order 8 and cutoff 1.05 cycles/cm, i.e. 75% of the Nyquit frequency) was applied to all projections, prior to reconstruction. Images were reconstructed using Filtered Backprojection. Uniform attenuation correction was applied. The SPECT images were rated visually by consensus by two neurologists experienced in neuroimaging (BAP, PPDD) and showed a relative hypoperfusion in the territories of the left middle (including the Broca area) and posterior cerebral arteries (Fig. 1). Eighteen months later, brain ECD-SPECT disclosed a significantly improved perfusion in the territories of the left middle and posterior cerebral arteries (Fig. 1).

Hematological routine laboratory findings were compatible with β-thalassemia minor showing decreased hemoglobin levels (12.6 g/dl), elevated red blood cell counts (6.08 10^{12}/l) with decreased mean cell volumes (62.9 fl) and almost normal mean corpuscular hemoglobin concentrations (33.0 g/dl). Morphological examination of red blood cells revealed a slight anisocytosis, poikilocytosis, microcytosis and target cells. Prothrombin time, partial thromboplastin time, antithrombin III and homocystine plasma levels were within normal limits. There was no evidence of a lupus anticoagulant. APC-r and mildly decreased levels of both proteins C and S were revealed repeatedly (table 1). APC-r and mildly decreased levels of protein S were found in a blood sample of the patient's mother as well (Table 1). Molecular diagnostic testing revealed heterozygosity for a pointmutation (G to A at position 1691) in exon 10 of the factor V gene for both the patient and his mother. By means of sequence analysis, no mutations were found in the *Pros1* gene. A treatment with 160 mg acetylsalicylic acid a day was started. The patient remained asymptomatic till now (follow-up period of 24 months).

Discussion

We described a 15-year-old boy with heterozygous β-thalassemia minor who presented recurrent

Table 1

Results for APC-r, protein S and protein C of the patient and his parents

	Results patient (d 0)	Results patient (d 14)	Results mother	Results father	Normal range
APC-r	1.59	1.55	1.5	> 2.0	> 2.0
Protein C	61.0%	61.0%	128.0%	113.0%	70-140%
Free Protein S	66.0%	67.0%	66.0%	96.0%	70-140%
Total Protein S	64.0%	65.0%	75.0%	106.0%	70-140%

Legend : d 0 = day of admission.

transient ischemic attacks. Acute phase brain perfusion SPECT significantly contributed to clinical diagnosis after structural neuro-imaging appeared to be not contributory. Performing SPECT early after onset of symptomatology is important as a long time interval between onset of transient ischemic attacks and SPECT imaging can decrease the detection sensitivity (Laloux, 1997). It has formerly been shown that Positron Emission Tomography is useful to improve detection of cerebral vasculopathy in patients with sickle cell anaemia (Powars *et al.*, 1999) but this case report is the first to demonstrate that perfusion SPECT is a useful and sensitive tool for detecting cerebrovascular events in patients with hemoglobinopathies as well.

As patients with heterozygous β-thalassemia minor usually are asymptomatic, we screened for risk factors of thrombophilia and revealed APC-r due to heterozygosity for factor V Leiden. Plasma levels of both proteins C and S were mildly decreased but one would expect lower values in case of protein C or protein S deficiency. It seems improbable that the thrombotic event itself caused the mild decrement of protein S and C seen confirmation of the latter by repeated analysis two weeks after the transient ischemic attack. Shirahata *et al.* (1992) reported slightly decreased plasma levels of both proteins S and C in a series of patients with however homozygous β-thalassemia intermedia and major. Decreased plasma levels were shown to be most pronounced for protein C as we observed in our patient as well. Although an explanation for this phenomenon is lacking so far, the authors postulated that these decreases might contribute to thrombophilia in thalassemic patients (Shirahata *et al.*, 1992). If this hypothesis is correct, an unique association of heterozygous β-thalassemia minor, heterozygosity for factor V Leiden and mildly decreased plasma levels of protein S and C, might have caused clinically significant thrombophilia resulting in the recurrent transient ischemic attacks our case displayed.

In conclusion, this case underlines the thrombogenic risk of heterozygous β-thalassemia minor in children heterozygous for factor V Leiden mutation. We therefore suggest to screen for thrombophilia in children with β-thalassemia minor when thromboembolism-related phenomena occur. By means of this unique case, we demonstrate that perfusion SPECT is a useful and sensitive tool for detecting cerebrovascular events in patients with hemoglobinopathies.

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