Factor V Leiden and Antiphospholipid Antibodies Are Significant Risk Factors for Ischemic Stroke in Children

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Background and Purpose—The association between ischemic childhood stroke and thrombophilia has been debated. We studied the prevalence of thrombophilia risk factors in 65 unrelated children with ischemic stroke compared with 145 control subjects.

Methods—Patients and control subjects were tested for antithrombin protein C and protein S deficiencies, the presence of antiphospholipid antibodies (APLA), factor V Leiden (FVL), G20210A polymorphism of factor II gene (FII G20210A), and C677T polymorphism of 5,10-methylenetetrahydrofolate reductase gene (C677T MTHFR).

Results—Of 65 children, 7 had a stroke in the neonatal/perinatal period and therefore were analyzed separately. Thirty-one of the remaining 58 patients with pediatric stroke (53.4%) were found to have at least 1 thrombophilia marker compared with only 25.5% of control subjects. None of the patients or control subjects had protein S or antithrombin III deficiency. The prevalence of protein C deficiency was higher among pediatric stroke patients than among control subjects, but the difference was not statistically significant (OR = 7, 95% CI 0.75 to 65.1). Heterozygous FII G20210A and homozygous MTHFR 677T were not associated with an increased risk for stroke (OR = 1.29, 95% CI 0.2 to 8.2; and OR = 1.06, 95% CI 0.4 to 2.7, respectively). In contrast, the presence of APLA was associated with a >6-fold risk of stroke (OR = 6.08, 95% CI 1.5 to 24.3), and the homozygosity for FVL increased the risk of stroke by almost 5-fold (OR = 4.82, 95% CI 1.4 to 16.5). Five patients with pediatric stroke had a combination of ≥2 thrombophilia markers, whereas none of the control subjects had a combination of the markers. Most of the patients with neonatal/perinatal stroke were found to have at least 1 thrombophilia marker.

Conclusions—These data suggest that the prevalence of thrombophilia markers is increased in children with stroke compared with control subjects and, specifically, that FVL and APLA contribute significantly to stroke occurrence.

Key Words: child stroke, ischemic thrombophilia

Stroke in children is significantly less common than stroke in adults and has a reported annual incidence rate of 0.63 to 1.2 per 100 000 children. The most common cause of ischemic stroke in children is thrombotic vessel occlusion; however, rare vasculopathies, metabolic disorders, or cardiac sources of embolism have also been reported. The association between hereditary protein S (PS) or protein C (PC) deficiency and childhood stroke is debatable: 2 case reports and 2 case-control studies showed a positive correlation between PS and PC deficiency and stroke, whereas other studies could not confirm this correlation.

Prothrombotic polymorphisms, such as the substitution of arginine with glutamine at amino acid residue 506 in coagulation factor V (factor V Leiden [FVL]) and a G-to-A transition at position 20210 of the 3’ untranslated region of the factor II gene (FII G20210A), have been found to be the most common risk factors for venous thromboembolism. Increased prevalence of FVL was observed in some reports on pediatric arterial thromboses and stroke, but these data were not confirmed in other studies. Similarly, the association between FII G20210A and childhood stroke is controversial. In addition, the homozygous state for the C-to-T transition at nucleotide 677 (C677T) polymorphism of 5,10-methylenetetrahydrofolate reductase (MTHFR) gene was not found to be a risk factor for stroke in children. At present, the presence of antiphospholipid antibodies (APLA) is associated with stroke in children and adults.

Because the association of genetic prothrombotic polymorphisms with pediatric stroke is currently inconclusive, we evaluated in this study the risks exerted by antithrombin (AT), PC and PS deficiencies, as well as the presence of APLA, FVL, FII G20210A, and MTHFR 677T, in 65 children with ischemic stroke.

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Subjects and Methods

Patients

The study population included 65 children with ischemic stroke who were diagnosed between 1994 and 1999 and referred to our tertiary referral center in Israel for the evaluation of thrombophilia. Among the 65 children studied, 7 children were from 7 families with familial stroke, whom we previously reported. In the remaining 58 children, no family history of stroke was documented. There was no difference in clinical features or outcome of stroke between the children with familial or nonfamilial stroke. Among the 58 families with nonfamilial stroke, 3 thrombotic events were documented. In 1 family with PC deficiency, the father had an acute myocardial infarction at the age of 40, and in 2 other unrelated families with APLA and FVL, the mothers had a history of deep venous thrombosis at the age of 18 and 23 years, respectively.

The definition of stroke included the presence of an acute thrombotic cerebrovascular event that manifested as hemiplegia, aphasia, visual or balance disturbance, or seizures. In all patients, the clinical diagnosis of ischemic stroke was confirmed with CT or MRI.

Control Subjects

One hundred forty-five control subjects were recruited from 2 surgical departments (Pediatric-Orthopedics and Pediatric General Surgery) and from the Pediatric Hematology Outpatient Clinic. Inclusion criteria for this group were elective surgery, trauma, or elective admission. Patients with sepsis, acute febrile illness, coagulation abnormalities, active cancer, or avascular bone necrosis were excluded. Among the 145 control subjects, only 89 (61%) were examined for the following plasma-derived coagulation tests: PC, PS, AT, and APLA, but not all of these 89 patients were also tested for DNA polymorphisms for technical reasons. Likewise, 118 control subjects (81%) were tested for DNA polymorphisms; however, not all of these described plasma-derived coagulation tests were undertaken in all patients. Finally, these 2 groups of control subjects included 62 individuals (43%) who were examined for both plasma-derived and DNA tests. Because there was no difference between the groups in control subjects who were examined for plasma-derived tests and those tested for DNA polymorphisms with regard to ethnic origin, sex, and age and because the tests performed for each control subject were performed at random, no selection bias was expected.

Coagulation Tests

Blood samples were obtained from all patients on referral at 1 month to 19 years after the acute stroke.

Nine parts of blood were drawn into 1 part of 3.8% sodium citrate. Citrated blood was centrifuged within 30 minutes at 2000 g (20 minutes), and plasma aliquots were stored at −35°C. PC and AT activities were measured with chromogenic assays (Baxter Dade), and free PS antigen was measured with enzyme-linked immunosorbent assay (Gradipore).

Patients were diagnosed with PC, PS, or AT deficiency if the value of the corresponding protein was <2 SD of the mean age-adjusted level. APLA levels were evaluated with at least 2 coagulation-based tests and 1 immunological test.

Coagulation-Based Tests

First, in the PTT-LA test (Diagnostica; Stago), circulating anticoagulant (CAC) was determined from the ratio of activated partial thromboplastin time with the use of reagent sensitive to the presence of CAC and a reagent insensitive to the presence of CAC (Actin FS; Dade). The normal ratios were calculated as the mean ± SD of 50 normal volunteers not taking oral anticoagulants and of 20 patients taking oral anticoagulants. Different ratios were established for each group. The presence of CAC was established if the ratio was >2 SD above the mean value (ie, >1.45).

Second, the dilute Russell’s viper venom test was determined as the ratio of dilute Russell’s viper venom time with the use of a reagent with a limited amount of phospholipids (LA Screen; Gradipore) to the time obtained with a reagent rich in phospholipids (LA Confirm; Gradipore). The normal ratios were calculated as the mean ± SD of 50 normal volunteers not taking oral anticoagulants and of 20 patients taking oral anticoagulants.

Immunological Test

The Synelisa Cardiolipin (IgG and IgM) Antibodies Enzyme Immunoassay Kit (Pharmacia & Upjohn Diagnostics) was used. The presence of antiphospholipid antibodies was established if the IgG or IgM level was >18 or >10 μ/mL, respectively.

All of the patients except 1 patient with perinatal stroke were tested initially for APLA 2 to 3 months after the acute ischemic stroke. The patient with perinatal stroke was tested 19 years after the acute event. Each patient was tested at least twice on 2 different occasions, and the diagnosis of APLA was established only if the second determination was positive. None of the patients was taking oral anticoagulants at the time of testing.

DNA Polymorphisms

DNA was extracted from EDTA-anticoagulant blood samples through standard methods. FVL was detected with polymerase chain reaction (PCR) amplification of a 267-bp fragment and MnlI digestion, as previously described. The C677T substitution in the MTHFR gene was identified with HindIII cleavage of a 198-bp PCR-amplified product as described by Frost et al. For identification of the G20210A substitution in the factor II gene, a slight modification of the method of Poort et al was used. A 253-bp fragment of the 3′ untranslated region of the gene was amplified through PCR with the same primers as described previously and digested simultaneously with HindIII and MspI. The A20210 and G20210 alleles were discernible with this procedure because the A20210 allele bears a restriction site for both enzymes, whereas the G20210 allele bears a restriction site for only MspI.

Statistical Analysis

A comparison of demographic characteristics between patients and healthy control subjects was made with χ2 test for categorical variables and Wilcoxon’s rank sum test for continuous variables. Univariate OR and 95% CI were estimated separately for each coagulation parameter test and DNA polymorphism. The OR and 95% CI of all variables were adjusted for age at tests through use of a multivariate logistic regression model. The statistical analysis was conducted only for pediatric stroke patients, whereas perinatal/neonatal stroke patients were presented separately. The prevalence of combination of factors was compared between patients and control subjects with the use of Fisher’s exact test.

Results

Sixty-five children with ischemic stroke met the inclusion criteria. Of those 65 patients, 58 were defined as pediatric stroke patients (diagnosis of stroke made after 1 month of age), and the remaining 7 cases were defined as perinatal/neonatal stroke patients (diagnosis of stroke made in the perinatal or neonatal period).

Perinatal/neonatal stroke is a unique entity. A combination of factors, some of them transient, may play a role in the cause of stroke during this period. Because the cause of stroke during the neonatal/perinatal period might be different from that of the pediatric stroke patients, the analysis was conducted separately for neonatal/perinatal and pediatric stroke patients.
Among the 58 children with childhood stroke and the 7 children with perinatal/neonatal stroke, none experienced recurrent stroke. In addition, no other thromboembolic events were documented among the entire group of 65 children.

Table 1 shows the demographic data for 58 pediatric stroke patients (neonatal/perinatal stroke excluded) compared with the control subjects. No significant differences in gender and ethnic origin were observed between patients and control subjects (\( P = 0.07 \) and 0.54, respectively). However, the mean age of the patients at the time of testing was lower than that of the control subjects (patients 7.2±6.5 years, control subjects 9.3±5.9 years, \( P = 0.007 \)).

The prevalence of thrombophilia markers among pediatric stroke patients and control subjects is shown in Table 2. To overcome the differences between the patients and control subjects with regard to age, this variable was included in a multivariate logistic regression model and the results presented in Table 2 were adjusted for age. Because no significant differences in gender and ethnic origin were observed between patients and control subjects, these variables were not included in a multivariate logistic regression model.

Thirty-one of 58 patients with pediatric stroke were found to have at least 1 thrombophilia marker. The prevalence of thrombophilia markers was higher among patients than among control subjects (56.8% and 25.6%, respectively). None of the patients or control subjects had PS or AT deficiency.

The diagnosis of PC deficiency was established if PC levels were <2 SD of mean PC levels adjusted for age. Two patients had PC levels of 54 to 56 and 48 to 53 U/dL measured at the age of 16 and 17 years, respectively. One patient had PC levels of 43 to 44 U/dL measured at the age of 13 years, and the remaining patient with PC deficiency had PC levels of 43 to 45 U/dL measured at the age of 7 years. One control had PC levels of 44 U/dL measured at the age of 15 years.

The prevalence of PC deficiency was higher among patients, but the difference was not statistically significant (OR=7, 95% CI 0.75 to 65.1). FII G20210A and homozygous MTHFR 677T were not associated with increased risk for stroke (OR=1.29, 95% CI 0.2 to 8.2; OR=1.06, 95% CI 0.4 to 2.7, respectively). In contrast, FVL increased in the risk of stroke by almost 5-fold (OR=4.82, 95% CI 1.4 to 16.5).

The presence of APLA was established if at least 1 of the coagulation-based or immunological tests described in Subjects and Methods was positive. Nine patients were found to

<table>
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<tr>
<th>TABLE 1. Demographic Data on Pediatric Stroke Patients and Control Subjects</th>
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<td><strong>Gender</strong></td>
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<td><strong>Origin</strong></td>
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<td>Arab</td>
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<tr>
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<td>Mean±SD, y</td>
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<tr>
<td>Range</td>
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<tr>
<td><strong>Age at diagnosis</strong></td>
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<tr>
<td>Mean±SD, y</td>
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<td>Range</td>
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<th>TABLE 2. Prevalence of Thrombophilia Markers in Pediatric Stroke Patients</th>
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<tr>
<td>PC</td>
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<td>APLA</td>
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<tr>
<td>FVL</td>
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<tr>
<td>FII G20210A</td>
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<tr>
<td>677T MTHFR*</td>
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</table>

*Only homozygotes for MTHFR 677T polymorphism were included.
†OR and CI values indicate statistical significance.
have APLA: 6 had increased ratios of CAC (range 1.6 to 2.1) and 3 had increased titers for anticardiolipin IgG (from 23 to 100 U/mL); 1 of them also had an increased titer for IgM (16 U/mL). Among the 6 patients with increased CAC ratios, 1 patient had also elevated anticardiolipin IgM (22 U/mL). The presence of APLA was associated with a 6-fold risk of stroke (OR = 6.08, 95% CI 1.5 to 24.3).

The distribution of demographic factors and the prevalence of thrombophilia markers among the 7 patients with perinatal/neonatal stroke are presented in Table 3. The ethnic origin of perinatal/neonatal stroke patients was similar to that of pediatric stroke patients or control subjects. Three patients were found to be homozygous for MTHFR 677T, and in 1 patient, a combination of APLA, FVL, and FII G20210A was detected. Combinations of >1 thrombophilia marker were observed only among the patient group and are presented in Table 4. A combination of PC deficiency and APLA was diagnosed in 1 patient (P = 0.005), and 2 additional patients were found to have 677T MTHFR homozygosity and FVL or FVL and FII G20210A, respectively (P = 0.08). Combinations of 3 thrombophilia factors were found in 2 additional patients: 677T MTHFR homozygosity, PC deficiency, and APLA were diagnosed in 1 patient with pediatric stroke (Table 4), and FII G20210A, FVL and APLA were detected in 1 patient with perinatal/neonatal stroke (Table 3).

In 8 of 58 patients with pediatric stroke, comorbid conditions were present at the time of stroke diagnosis. One patient who did not have thrombophilia markers had unilateral carotid stenosis. Two patients, 1 with PC deficiency and 1 with FVL, underwent surgery for correction of tetralogy of Fallot. Two additional patients, each with 677T MTHFR homozygosity, presented with dehydration and multitrauma at the time of stroke occurrence. The remaining 3 patients (1 with homozygous 677T MTHFR, 1 with PC deficiency, and 1 with a combination of FVL and FII G20210A) were diagnosed with bacterial sepsis. Thus, in 7 of 8 patients with comorbid conditions, thrombophilia was diagnosed.

Discussion

The present study is a retrospective case-control analysis of the risks exerted by hereditary and acquired thrombophilia factors. The retrospective nature of the study may result in some selection bias.

In the present study, FVL was found to be associated with an almost 5-fold increased risk of pediatric stroke (OR = 4.82, 95% CI 1.4 to 16.5). FVL was found in only 1 of 7 children with perinatal/neonatal stroke; this patient had also APLA and FII G20210A. Due to the small number of patients in this subgroup, the role of FVL in the cause of perinatal/neonatal stroke remains unknown.

The present data on FVL are in accordance with 4 other similar case-control studies in which FVL was found to be associated with pediatric stroke. In contrast, FVL was not found to be a risk factor for pediatric or neonatal stroke in another study. The difference among the studies can stem from the relatively small number of patients included in each study, the different ethnic background of the patients, and the clinical heterogeneity of patients with stroke.

In the present study, FVL was found to be associated with an almost 5-fold increased risk of pediatric stroke (OR = 4.82, 95% CI 1.4 to 16.5). FVL was found in only 1 of 7 children with perinatal/neonatal stroke; this patient had also APLA and FII G20210A. Due to the small number of patients in this subgroup, the role of FVL in the cause of perinatal/neonatal stroke remains unknown.

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In contrast to children, none of the reports that evaluated ischemic stroke in adults found an association between FVL and stroke. It has been suggested that the presence of FVL contributes more to the risk of stroke in children than in adults, probably due to the presence of an additional risk factor specific for children, such as paradoxical embolism through a patent foramen ovale.

Similar to FVL, APLA was associated with a 6-fold increase in the risk of pediatric stroke in the present study.

**TABLE 3. Characteristics of Perinatal/Neonatal Stroke Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Origin</th>
<th>Sex</th>
<th>Age at Testing</th>
<th>AT, U/dL</th>
<th>PC, U/dL</th>
<th>PS, U/dL</th>
<th>APLA</th>
<th>FVL</th>
<th>FII G20210A</th>
<th>MTHFR 677T*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mixed</td>
<td>F</td>
<td>19 y</td>
<td>106</td>
<td>81</td>
<td>109</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Asia Africa</td>
<td>M</td>
<td>3 mo</td>
<td>84</td>
<td>74</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Mixed</td>
<td>M</td>
<td>1.25 y</td>
<td>107</td>
<td>89</td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Europe America</td>
<td>F</td>
<td>1.42 y</td>
<td>96</td>
<td>92</td>
<td>80</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Europe America</td>
<td>F</td>
<td>1 mo</td>
<td>105</td>
<td>48†</td>
<td>72</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>Europe America</td>
<td>F</td>
<td>10 mo</td>
<td>85</td>
<td>68</td>
<td>79</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Europe America</td>
<td>M</td>
<td>2 mo</td>
<td>87</td>
<td>78</td>
<td>83</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Normal range 80–125 70–130 65–135

+ indicates present; —, absent.

*Homozygotes for MTHFR 677T polymorphism.

†Normal range adjusted for 6 mo: 37–81 U/dL.

**TABLE 4. Prevalence of Combinations of Thrombophilia Factors Among Pediatric Patients and Control Subjects**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Patients</th>
<th>Control Subjects</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>PC/APLA</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1*</td>
</tr>
<tr>
<td>FVL/MTHFR/FII G20210A</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

*The patient presented with a combination of PC deficiency, APLA, and 677T MTHFR homozygosity.
These data are consistent with those of the study of De Veber et al., who established an 8-fold increase in the prevalence of antithrombin antibodies in children with stroke compared with the control subjects. In contrast, McColl et al. did not find an increased prevalence of antithrombin antibodies in children with stroke. In the present study, APLA were tested with 3 different tests, thereby increasing the sensitivity of the detection of the antibodies. In contrast, in other studies, where APLA was evaluated with only 1 test, the diagnosis of APLA could have been missed in some patients. Further studies with similar diagnostic tests for APLA are needed to elucidate the role of these antibodies in the pathogenesis of pediatric stroke.

Similar to the case-control study of McColl et al., no association between hereditary AT, PS, and PC deficiencies and childhood stroke was established in the present study. However, in other reports, such an association was found. Deficiencies of AT, PC, and PS are rare defects, and most of the studies that analyzed their effect on stroke were not powerful enough to detect a risk. At the present, therefore, the role of these thrombophilia factors in ischemic pediatric stroke remains debatable.

FII G20210A and homozygous 677T MTHFR have not been found to confer a risk of stroke in the present patients. These results are similar to those reported in 2 recent studies by McColl et al. and Zenz et al., in which no association was found between FII G20210A or 677T MTHFR and stroke. This is in contrast to a recent study by Nowak-Gottl et al. Three of 7 patients with perinatal/neonatal stroke were found to be homozygous for 677T MTHFR. However, due to the small number of patients in this group, the association between this polymorphism and the occurrence of stroke cannot be determined. In 1 patient with perinatal stroke and a combination of FVL, FII G20210A, and APLA, the diagnosis of APLA was made 19 years after the stroke, so the causality between APLA and perinatal stroke cannot be established with certainty in this patient.

The combination of thrombophilia markers increased the risk of stroke in our patients. At least 2 thrombophilia markers were observed in 3 of 58 patients with pediatric stroke and in 1 of 7 patients with perinatal stroke, whereas no combinations were detected in the control subjects. Two patients had a combination of 3 thrombophilia markers, 1 with perinatal/neonatal stroke. Because the number of patients affected by combined defects was small, we could not compute the attributable risk of stroke for each combination.

Among 8 pediatric stroke patients with underlying comorbid conditions at the time of stroke diagnosis, 7 also had thrombophilia markers. Comorbid situations such as immobilization, surgery, or sepsis are well established acquired hypercoagulable states that are associated with an increased risk of thrombosis. Thus, it is possible that an interaction between these hypercoagulable states and thrombophilia factors occurred, enhancing even further the profile of hypercoagulability, and resulting in the occurrence of stroke in these patients.

In conclusion, childhood stroke appears to be a diverse condition with many potential risk factors. The results of the present study demonstrate that the “thrombophilia burden” is definitely increased in children with ischemic stroke. To date, the guidelines for the anticoagulant treatment of children with stroke and thrombophilia are limited. In view of our results, the screening of children with ischemic stroke for thrombophilia markers seems to be justified. The identification of thrombophilia factors may warrant prophylactic anticoagulant therapy in conditions associated with high risk of thrombosis. Moreover, in some of the patients with a combination of risk factors, anticoagulant therapy should be considered.

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References


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