Evaluation of cases with cerebral thrombosis in children

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Abstract

Aim: We aimed to evaluate the patients who were followed up in our clinic with a diagnosis of cerebral sinovenous thrombosis in terms of age, sex, clinical findings, etiology, thrombophilic factors, imaging findings, treatment and prognosis.

Material and Methods: The files of 11 patients who were followed up in our pediatric neurology clinic with a diagnosis of cerebral thrombosis between 1 December 2010 and 31 December 2014 were retrospectively analyzed.

Results: Seven of 11 patients were male (63.6%). The median age was 14 years (2-17 years). Six (54%) of the patients presented with a complaint of headache. Other complaints at presentation included diplopia (n:3), weakness and difficulty in speaking (n:1) and seizure (n:1). A diagnosis of pseudotumor cerebri was made in eight of the patients (72.7%). In the etiology, mastoiditis was found in three patients, mastoiditis and meningitis were found in combination in one patient, Behçet's disease was found in three patients and head trauma was found in one patient. In 3 patients, only prothrombotic genetic risk factors were present; one patient had deficiency of protein C and S, one patient had deficiency of antithrombin III and one patient had hyperhomosisteinemia in association with vitamin B12 deficiency. 1A homozygous MTFHR A1298C mutation was detected in the patient who had mastoiditis and meningitis and protein S deficiency and lupus anticoagulant were found in another patient who had mastoiditis. All patients received anticoagulant treatment and all patients recovered without neurological sequelae except one.

Conclusions: Cerebral sinovenous thrombosis should be considered in patients who present with headache and focal neurological deficits. Appropriate utilization of imaging studies is necessary for the diagnosis. Detailed ear, nose and throat examination should be performed to detect mastoiditis. It is recommended that genetic risk factors should be investigated, because hereditary thrombophilic factors may have a role in children. Behçet's disease which is relatively common in our country should be considered in differential diagnosis. (Turk Pediatri Ars 2016; 51: 87-93)

Keywords: Anticoagulant therapy, cerebral thrombosis, child

Introduction

The prevalence of cerebral thrombosis which is observed rarely in the pediatric age group ranges between 0.4/100 000 and 0.7/100 000 children and 40% of all pediatric cases are newborns (1-3). Recognition of thrombosis mostly as a disease of adulthood, presence of different underlying clinical conditions and variable symptoms cause difficulty in diagnosis in the childhood. Although the diagnosis is made more easily because of the imaging techniques which have advanced in recent years and because of increased awareness, the effect of the underlying factors on development of thrombosis, treatment and the risk of relapse have not been fully elucidated in the pediatric age group.

Thrombosis is a multifactorial event. It usually develops with association of hereditary and acquired risk factors (4-6). Infections, dehydration and some types of anemia (sickle cell anemia, severe iron deficiency anemia) which are commonly observed in the pediatric age group, congenital heart diseases, nephrotic syndrome, systemic lupus erythematosus and malignancies are among the causes of thrombosis. In addition to these systemic risk factors, head and/or neck traumas, central nervous system tumors and venous stasis occurring after intracranial surgery may also lead to thrombosis (7). Prothrombotic genetic risk factors are found in 24-64% of the cases in the pediatric age group (more common compared to adults) (2, 8-12). Therefore, prothrombotic genetic risk factors should be investigated in pediatric cases of thrombosis.
The clinical symptoms observed in cases of cerebral thrombosis are not specific and may be overlooked. Headache due to increased intracranial pressure (ICP) is the most common cause of presentation. Seizures, alterations in consciousness, encephalopathy, focal neurological findings (cranial nerve palsies, hemiparesis, sensory loss) may also be observed (7, 13). Clinicians should be suspicious in any kind of acute neurological event and request necessary tests for making the diagnosis and adjusting treatment early.

In this study, the patients whom we followed up with a diagnosis of cerebral thrombosis in our clinic are presented and age and gender distribution, clinical findings, etiology, imaging findings, treatment and prognoses are discussed.

Material and Methods

The medical records of 11 patients aged between 2 and 17 years (median age: 14 years) who were diagnosed with cerebral thrombosis between December the 1st, 2010 and December 31st, 2014 in Marmara University, Pendik Training and Research Hospital were retrospectively examined in terms of age, gender, clinical findings, etiology, risk factors predisposing to thrombosis, imaging findings, treatment and prognosis. Neonatal patients who have different etiology, clinical presentation and prognosis were excluded from the study. Ethics committee approval was obtained from Marmara University School of Medicine on 11/06/2015 with number 09.2015.311 for the study.

A diagnosis of cerebral thrombosis was made with brain magnetic resonance imaging (MRI) and brain magnetic resonance venography (MRV). Demonstration of complete or partial filling defect in at least one or more sinuses was considered sufficient for making the diagnosis. Biochemical and molecular tests were performed in all patients to elucidate the etiology. These tests included C-reactive protein, erythrocyte sedimentation rate, complete blood count, protein C, protein S, antithrombin 3, d-dimer, lactate, homocysteine, antinuclear antibody (ANA), extractable nuclear antigen antibody (ENA) profile, antiphospholipid and/or anticardiolipin antibodies, factor V Leiden mutasyonu, prothrombin 20210 gene mutation, methylenetetrahydrofolate reductase (MTFHR) gene mutation, lupus anticoagulant, prothrombin time (PT) and activated partial thromboplastin time (aPTT). Cerebrospinal fluid (CSF) opening pressure was measured by way of lumbar puncture (LP) and biochemical and culture examinations were performed in cases of clinical necessity. In patients in whom Behçet’s disease was considered, Pathergy test was performed and dermatologic and opthalmological consultations were required.

Statistical analysis

Statistical Package for the social sciences 20.0 (SPSS Inc.; Chicago, IL, USA) program was used for all descriptive statistical analyses. The continuous variables were expressed as mean±standard deviation.

Results

Seven of eleven patients were male (63.6%). The median age was 14 years (2-17). Six of the patients (54.5%) presented with the complaint of headache. Other causes of presentation included diplopia (n=3), aphasia, loss of strength (n=1) and seizure (n=1). Papilledema was found in eight (72.7%) patients on neurological examination. Nervus abducens palsy accompanied in two of these patients. Lethargy, aphasia and hemiparesis were found in one patient. Venous infarction was present on magnetic resonance imaging in this patient. Brain parenchymal lesion was not found in the other patients. It was the first attack of all patients except for one patient. A patient aged 14 years who presented because of repeated thrombosis was followed up two years ago in another center because of cerebral thrombosis and received anticoagulant treatment for six months. A diagnosis of Behçet’s disease was made in this patient. Thrombosis was found in a single sinus in six of the patients and in two or more sinuses in the remaining patients. Thrombosis was found in the transverse sinus in two patients. Thrombosis was found in the sigmoid sinus in three patients and in the cortical veins in one patient. Thrombosis was present in the transverse and sigmoid sinuses in three patients, in the transverse and sagittal sinuses in one patient and in all three sinuses in one patient.

In the etiology, mastoiditis was found in three patients, mastoiditis and meningitis were found in one patient, Behçet’s disease was found in three patients and head trauma was found in one patient. In the remaining patients, only genetic prothrombotic factors were present in the etiology. Protein C and S deficiency was found in one patient (protein C 59.95%, reference: 70-130%, protein S 17.6%, reference: 89-129%), antithrombin 3 deficiency was found in one patient (47%, reference 80-120%) and hyperhomocysteinemia (349.4 mol/L reference: 4.3-9.9) and accompanying vitamin B12 deficiency (59 pg/mL, reference 180-914) was found in one patient. In this patient who had hyperhomocysteinemia, heterozy-
Heterozygous MTFHR A1298C and heterozygous MTFHR C677T mutations were found. Homozygous MTFHR A1298C mutation was found additionally in the patient who had mastoiditis and meningitis and protein S deficiency and lupus anticoagulant were found in another patient who had mastoiditis. The D-dimer result could not be reached in four patients; the D-dimer values in the remaining patients ranged between 0.24 and 3.68 µg/mL (0-0.5). The D-dimer value was high in two patients. One of these patients had hyperhomocysteinemia and the other one was diagnosed with Behçet’s disease.

All patients received low molecular weight heparin by the subcutaneous route in the acute period. Oral warfarin was given to the patient who had Behçet’s disease and the other patients received low molecular weight heparin by the subcutaneous route as anticoagulant treatment for 6 months. It was recommended that treatment should be continued with lifelong aspirin in one patient who had lupus anticoagulant and protein S deficiency.

Intravenous antibiotic treatment with third generation cephalosporins was given for 10 days to the patients who had mastoiditis (n=3). When clinical response could not be obtained in the patient who had mastoiditis and meningitis, vancomycin and imipenem treatment was given for 14 days and mastoidectomy was performed additionally. Acetazolamide treatment was initiated in the patients who had a clinical picture of pseudotumor cerebri and increased CSF pressure (n=8). Treatment was continued for 6-12 months until clinical improvement was observed.

The patients who were diagnosed with Behçet’s disease received high dose steroid by the intravenous route in the acute period. Afterwards, treatment was continued with oral prednisolone (1 mg/kg), azathioprine (100 mg/day) and monthly intravenous cyclophosphamide (750 mg/dose) in one patient, with oral prednisolone, azathioprine and colchicine (1.5 mg/day) in another patient and with oral prednisolone and azothioprine in the third patient.

### Table 1. Demographic properties of the subjects

<table>
<thead>
<tr>
<th>Number</th>
<th>Age</th>
<th>Gender</th>
<th>Complaint</th>
<th>Neurologic</th>
<th>Localization examination</th>
<th>Parenchymal</th>
<th>Emboliology finding</th>
<th>Previous Follow-up thrombosis</th>
<th>Prognosis period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>F</td>
<td>Diplopia</td>
<td>Papilledema</td>
<td>Transverse sinus</td>
<td>Absent</td>
<td>Protein C and S deficiency</td>
<td>Absent</td>
<td>6 months</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>M</td>
<td>Headache, vomiting, fever</td>
<td>Papilledema</td>
<td>Sigmoid sinus</td>
<td>Absent</td>
<td>Mastoiditis, Meningitis, Homozygous MTFHR A1298C mts</td>
<td>Absent</td>
<td>6 months</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>M</td>
<td>Diplopia, blurred vision</td>
<td>6th nerve palsy, Papilledema</td>
<td>Sigmoid sinus</td>
<td>Absent</td>
<td>Mastoiditis</td>
<td>Absent</td>
<td>6 months</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>M</td>
<td>Clouding of consciousness, aphasia</td>
<td>Lethargia, Aphasia, obscure hemiparesis</td>
<td>Cortical veins</td>
<td>Venous infarction</td>
<td>B12 deficiency, Hyperhomocysteinemia, Heterozygous MTFHR A1298C mts, Heterozygous MTFHR C677T mts</td>
<td>Absent</td>
<td>8 months</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>F</td>
<td>Headache strabismus</td>
<td>Papilledema, 6th nerve palsy</td>
<td>Sigmoid sinus, transverse sinus,</td>
<td>Absent</td>
<td>Mastoiditis</td>
<td>Absent</td>
<td>6 months</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>F</td>
<td>Diplopia</td>
<td>Papilledema</td>
<td>Transverse sinus, sigmoid sinus</td>
<td>Absent</td>
<td>Mastoiditis, Protein S deficiency, Lupus anticoagulant</td>
<td>Absent</td>
<td>1 year</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>M</td>
<td>Seizure</td>
<td>Spasticity</td>
<td>Transverse sinus, sagittal sinus</td>
<td>Present</td>
<td>Trauma</td>
<td>Absent</td>
<td>6 months</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>F</td>
<td>Headache</td>
<td>Normal</td>
<td>Transverse sinus, sigmoid sinus</td>
<td>Absent</td>
<td>Antithrombin deficiency</td>
<td>Absent</td>
<td>18 months</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>M</td>
<td>Headache, dizziness</td>
<td>Papilledema</td>
<td>Sigmoid sinus</td>
<td>Absent</td>
<td>Behçet’s disease</td>
<td>Present</td>
<td>24 months</td>
</tr>
<tr>
<td>10</td>
<td>17</td>
<td>M</td>
<td>Headache, blurred vision</td>
<td>Papilledema</td>
<td>Transverse sinus, sigmoid sinus, sagittal sinus</td>
<td>Absent</td>
<td>Behçet’s disease</td>
<td>Absent</td>
<td>6 months</td>
</tr>
<tr>
<td>11</td>
<td>16</td>
<td>M</td>
<td>Headache</td>
<td>Papilledema</td>
<td>Transverse sinus</td>
<td>Absent</td>
<td>Behçet’s disease</td>
<td>Absent</td>
<td>18 months</td>
</tr>
</tbody>
</table>
The mean follow-up period of the patients was 10.5 months (6-24 months). In the follow-up during which neurological examination and brain MRI and MRV were performed with three-month intervals, thrombosis was found to have completely improved at the end of three months in seven patients, partial improvement was found in three patients and encephalomalacia in the left frontotemporal region in association with partial improvement was found in one patient in whom thrombosis was observed because of trauma. The demographic properties of the patients are summarized in Table 1. Treatment was not changed in the patients with normal neurological examination in whom partial improvement was found.

Discussion
In our study, thrombosis was found more frequently (63.6%) in the male patients and this findings was compatible with the literature (1, 10, 14-17). The median age of occurrence of thrombosis was 14 years. In the literature, the median age has been found to be approximately 2-fold higher according to the studies including patients who were in the post-neonatal period (18, 19). The most common cause of presentation was headache. Diplopia was the second most common cause of presentation. Papilledema was found on neurological examination in all patients who presented because of headache except for one patient. Headache is the most common symptom in the literature and has been reported with a frequency of 90% in adults (20) and with a frequency of 60% in children after the neonatal period (2). The frequency of papilledema has been reported to be 25-50% in adults and children in the literature. It was observed with a higher rate in our study (2, 20, 21). Altered consciousness, aphasia and focal findings were present in one patient who was found to have venous infarction secondary to cortical vein thrombosis. Seizure was observed in a two-year old patient who developed thrombosis following trauma. In the literature, cerebral thrombosis has been usually manifested with seizure and focal signs in infants and young children, whereas headache has been reported with a higher rate and altered consciousness and seizures have been reported more rarely in older children (15).

In the etiology, genetic prothrombotic factors were found in five patients. The two most common prothrombotic conditions were protein S deficiency and MTFHR A1298C mutation. In the literature, prothrombotic factors have been found with a rate of 24-64% in children in the post-neonatal period (1, 2, 8, 10-12). Conditions including head and neck traumas and infection (especially sinusitis, mastoiditis, meningitis) are in the first orders in the etiology (18, 19, 22). In our series, mastoiditis was observed in four patients. Behçet’s disease was observed in three patients in our study, though it has not been reported frequently in the literature. In a study conducted in our country, Bektaş et al. (23) described Behçet’s disease in two of six patients with thrombosis aged outside the neonatal period. Therefore, Behçet’s disease should be absolutely included in the differential diagnosis in areas where this disease is observed relatively frequently and patients should be interrogated in this aspect.

Homocysteine is an amino acid which is formed as an intermediate product in transformation of methionine to cystathionine. It is transformed back to methionine or cysteine with the help of group B vitamins. Increased homocysteine levels are known risk factors for cardiovascular diseases and formation of thrombosis (24). Deficiencies of group B vitamins (B6, folic acid, B12) and genetic deficiency of MTFHR enzyme which is involved in transformation of folate to its active form are risk factors for hyperhomocysteinemia (25). Especially two known polymorphisms of the MTFHR gene (MTFHR C677T and A1298C) have been associated with increased homocysteine levels (26). However, a direct relation of gene mutations with thrombosis has not been demonstrated, although it is known that MTFHR gene mutations are a reason for hyperhomocysteinemia and hyperhomocysteinemia is a risk factor for formation of thrombosis (25).

The radiological investigations which should be performed for a diagnosis of cerebral thrombosis include brain MRI and MR venography. In suspicious cases and in patients in whom only cortical veins are involved, cerebral conventional angiography which evaluates venous patency of the vascular bed and to prevent extension of thrombosis and formation of new thrombosis after acute treatment (13). In the pediatric case series published in the last decade, antithrombotic agents used follow-
ing the diagnosis of cerebral thrombosis show variance (7). Different treatment protocols are used in different centers. In the acute phase, heparin, low molecular weight heparin or oral warfarin are preferred; after the acute phase anticoagulant treatment is continued for 3-6 months with low molecular weight heparin or oral warfarin (7). In single-center or minor multi-center cases series, it was reported that treatment with intravenous or subcutaneous low molecular weight heparin followed up with anti-factor Xa antibody levels was safe (10, 29, 30).

All our patients received acute treatment with low molecular weight heparin for 7-10 days and then prophylactic anticoagulant treatment for 6 months. Treatment was continued with aspirin in one patient who had lupus anticoagulant and protein S deficiency. No relapse was observed in the one-year follow-up period.

Antibiotic treatment with intravenous second or third generation cephalosporins is recommended in cases of cerebral thrombosis related with otitis media and mastoiditis (7). Although mastoidectomy, myringotomy and/or placement of tympanostomy tube have not been proven to contribute to treatment, these interventions are preferred by otolaryngologists (31). In our study, all patients who had cerebral thrombosis related with mastoiditis received antibiotic treatment and mastoidectomy was also performed in these patients.

Long-term acetozolamide treatment may be needed in patients presenting with a clinical picture of pseudotumor cerebri; lumboperitoneal shunt may be placed in patients who are unresponsive to treatment. In our series, no patient needed shunt and the patients who had a picture of pseudotumor cerebri received long-term acetozolamide treatment until increased intracranial pressure findings disappeared and the CSF pressure returned to normal.

In our study, no mortality occurred in a mean follow-up period of 10.5 months (6-24 months). Permanent neurological damage developed only in one patient. This patient was a two-year old patient who had intracranial hemorrhage due to head trauma and was found to have hydrocephaly and thrombosis in the sagittal sinus. Severe spasticity was present on neurological examination and the patient was receiving antiepileptic treatment because of resistant seizures. Full clinical recovery occurred in the patients who were found to have complete and partial improvement in thrombosis. Methylenetetrahydrofolate reductase A1298C and heterozygous MT-FHR C677T mutations were present in the patient who had venous infarction and homocysteinemia. On brain MRI performed in the third month in this patient, encephalomalacia was found, but neurological examination was found to be normal. In the pediatric age group, the mortality rate related with cerebral sinovenous thrombosis is below 10%, but neurological defects may be observed at the time of discharge or during the follow-up in 17-79% of the patients; long-term rehabilitation may be needed because of motor and cognitive sequelae (2, 10, 18, 32-34). Young age, coma, seizure and focal neurological findings have been found to be related with poor prognosis (2). Headache, vision disorders and 6th cranial nerve palsy related with increased intracranial pressure may be observed in the long-term despite anticoagulant treatment, use of antibiotics and surgical treatment when necessary (7). In three studies in which recanalization was evaluated in children, recanalization was not found in 11-16% of the patients (1, 10, 17). Therefore, patients with cerebral thrombosis should be closely monitored in terms of neurological and ophthalmologic symptoms and follow-up brain imaging should be performed in the first one year in terms of persistence, progression and recanalization of thrombosis or venous stenosis. Some centers repeat brain imaging in the 3, 6 and 12th months following discharge as MRI and MRV (7). We also repeated brain imaging in the 3, 6. and 12th months in our patients. Although recanalization is a significant treatment objective in venous thrombosis, it has been reported to have no effect on the prognosis (22). Prophylactic anticoagulant treatment may be terminated in three months, if recanalization is observed in the early period (7). We continued prophylactic anticoagulant treatment for six months in our patients.

Relapse is observed in 10-20% of the cases of pediatric cerebral thrombosis and approximately half of these cases are systemic (1, 2, 17, 10). Kenet et al. (17) reported that the risk of relapse is high in children aged older than two years in presence of G20210A mutation and in cases where recanalization is absent. Patients with a risk of relapse should be evaluated individually and secondary anticoagulant prophylaxis should be initiated (17). In our study, no relapse was observed. However, the fact that a patient with a diagnosis of Behçet’s disease who could not be diagnosed at the first attack presented with a second cerebral thrombosis attack showed that relapse might occur when the underlying disease persisted.

In conclusion, the diagnosis of cerebral thrombosis is overlooked in the pediatric age group, because it occurs
rarely and may present with different neurological symptoms. In presence of accompanying risk factors, cerebral sinus venous thrombosis should be kept in mind in patients presenting with headache and focal neurological deficit; MRI and MRV should be ordered in the early period in case of suspicion.

Ethics Committee Approval: Ethics committee approval was received for this study from Marmara University School of Medicine (06/11/2015 - 09.2015.311).

Informed Consent: Informed consent was not obtained due to retrospective nature of this study.

Peer-review: Externally peer-reviewed.


Conflict of Interest: No conflict of interest was declared by the authors.

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