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Epileptic seizures in Neuro-Behcet disease: Why some patients develop seizure and others not?

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ABSTRACT

Purpose: Behcet disease (BD) is a chronic relapsing inflammatory disorder. Neuro BD (NBD) is seen in approximately 5% of all patients. The aim of this study is to investigate the frequency, type and prognosis of epileptic seizures in different forms of NBD.
Methods: All files of 42 patients with NBD were evaluated between 2006 and 2012, retrospectively. The demographic data, the presentation of NBD, clinical findings including seizures, EEG and neuroimaging findings were reviewed.
Results: The mean age of patients was 35.02 ± 8.43 years. Thirty (71.4%) patients were male; the remaining 12 of them were female. Twenty-four patients had brainstem lesions; 16 patients had cerebral venous thrombosis. Spinal cord involvement was seen in two patients. Seven patients had epileptic seizures (six partial onset seizures with or without secondary generalization). Six of them had cerebral sinus thrombosis (CVT). Four patients had a seizure as the first symptom of the thrombosis. One patient had late onset seizure due to chronic venous infarct. The other patient with seizure had brainstem involvement. The remaining was diagnosed as epilepsy before the determination of NBD.
Conclusion: CVT seen in BD seems to be the main risk factor for epileptic seizures in patients with NBD. The prognosis is usually good especially in patients with CVT. Epileptic seizures in patients with brainstem involvement may be an indicator for poor prognosis. Superior sagittal thrombosis or cortical infarct would be predictor of seizures occurrence because of the high ratio in patients with seizures.

1. Introduction

Behcet's disease (BD) is a chronic relapsing inflammatory disease of unknown etiopathogenesis [1–3]. It is a disorder of young adults with male predominance. There is a geographical variation in prevalence [4]. Hulusi Behcet, Turkish dermatologist, first described it [2]. BD is mainly characterized by oral and genital ulcerations, ocular manifestations and by involvement of the gastrointestinal, cardiovascular, pulmonary, skeletal and central nervous system [1]. Recurrent oral ulceration is prerequisite with any two of genital ulcerations, skin lesions, uveitis and hyperactivity of skin to nonspecific physical insult (Patergy test) according to the diagnostic criteria formed by the International Study Group [5].

Neurologic manifestation in BD (NBD) is involved in about 5–10% of the patients with BD [3,6]. There are two major forms of neurologic involvement of BD according to the clinical and imaging examination. The first, which is seen in the majority of patients, may be characterized as a vascular-inflammatory central nervous system (CNS) disease with focal or multifocal parenchymal involvement, mostly presenting with a brainstem syndrome (intra-axial NBD); the other, which has few symptoms and a better neurologic prognosis, may be caused by isolated cerebral venous sinus thrombosis and intracranial hypertension (extra-axial NBD), occurring in up to 20% of the cases. Spinal cord involvement, arterial CNS involvement, optic neuritis, aseptic meningitis, and peripheral neuropathies may be seen as a presentation of NBD, but are rare [3,7].

Epileptic seizure in NBD was observed rarely in previous studies [8,9] Different seizures types such as partial seizures, generalized tonic clonic seizures; myoclonic jerks, epilepsia partialis continua and status epilepticus were reported [8–12]. The aim of this study is to investigate the frequency, type and prognosis of epileptic seizures in different forms of NBD.

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2. Methods

All files of 42 patients with NBD were reviewed retrospectively in Ankara Research and Training Hospital, Department of Neurology between January 2006 and December 2012, retrospectively. The demographic data, the presentation of NBD, clinical findings including seizures, cerebrospinal fluid (CSF) examination, electroencephalography (EEG) and neuroimaging finding were reviewed. Seizures were classified according to the criteria of International League Against Epilepsy [13]. The diagnosis of NBD was revised according to the International Consensus Recommendation (ICR) Criteria for NBD during the retrospective analysis [14]. The clinical course of epileptic seizures and NBD were also evaluated.

3. Results

The mean age of patients was 35.02 ± 8.43 years. Thirty (71.4%) patients were male; the remaining twelve (28.6%) of them were female. All of the patients had definite NBD according to the ICR criteria. Twenty-four (57.1%) patients with NBD had CNS parenchymal involvement with brainstem-diencephalic regions. CVT was present in sixteen (38.1%) while two patients had only spinal cord involvement (5.8%).

Seizures were observed in seven (16.7%) of 42 patients. Demographic data, clinical features, seizure type, CSF findings, EEG, magnetic resonance imaging findings and prognosis are shown in Table 1. The mean age was 30.43 ± 9.36 years (age range 24–49). Only one patient with seizure was female, the remaining six (85.7%) patients were male. Mean age at the diagnosis of BD 27.0 ± 8.68 (16–42 years) years. The patients with epileptic seizures were followed up between 3 months and 5.5 years (mean: 32.14 ± 22.37 months). In their medical history, six patients had no risk factors regarding the epilepsy; only one patient had the family history for epilepsy. The mean duration of NBD in patients without seizures was 30.34 ± 22.24 months.

CVT was observed in six patients with epileptic seizure. Cranial magnetic resonance imaging and venography was performed to all patients. Superior sagittal thrombosis was present in four patients (66.7%) while two patients had left transverse sinus thrombosis (Fig. 1A and B). However, the ratio of superior sagittal thrombosis was 40% when the patients diagnosed as CVT without seizures were analyzed.

Among the patients with CVT, five of them had complex partial seizures and three of them had also secondary generalized tonic clonic seizures (SGTCS). Four patients had seizures as the first symptom of the thrombosis. One patient had late onset seizure probably due to chronic venous infarction in left temporal–parietal region seven weeks after the diagnosis of NBD disease. The seizures of other patient were started three months before the determination of thrombosis.

Patient 1 and 2 had only one partial onset and SGTCS seizure at admission. They were treated with carbamazepine and levetiracetam, respectively and antiepileptic drugs were stopped 6 and 8 months of treatment. No seizure was seen in their follow up. Their EEGs were also normal. Patient 3 had two complex partial seizures, whereas three partial onset and SGTCS was present in Patient 4. They were treated oxcarbazepine and carbamazepine during 24 months, respectively. The dose of antiepileptic drug was decreased in Patient 3 and 4 and termination of treatment is planned for them. 4–7 Hz slow waves were seen in their first EEG and recurrent EEG examinations were normal. Seizure was not recurred in both of patients. Patient 5 (only female patient) had venous infarction and she was admitted to the hospital with complex partial status epilepticus seven weeks after the diagnosis of CVT. Left temporal seizure activity was also observed in her EEG. Firstly, phenytoin infusion was applied to her and then phenytoin therapy was continued. She was followed up during 66 months after the seizure. The treatment was changed from phenytoin to oxcarbazepine, because she was planning pregnancy. No seizure was occurred before, during and after pregnancy. We decided to terminate the treatment after 52 months from the seizure beginning and decreased the dosage. However, complex partial seizure was started again and the dosage was increased. Recurrent EEG also showed us left temporal sharp waves (Fig. 2). Myoclonic and one generalized tonic clonic seizure (GTCS) were present in

Table 1
Demographic data, clinical features, seizure type, CSF findings, EEG, magnetic resonance imaging findings and prognosis of patients.

No	Age year	Sex	AgeDx BD year	NBD type	Relation NBD	Seizure type	CSF	Clinical manifestation	EEG	MRI MRV	Follow up month	Outcome
1	25	M	24	CVT	Attack	Partial onset SGTCS	–	Headache Papilledema	1.N 2. N	SSS Thrombosis	35	Seizure free AED stopped
2	37	M	35	CVT	Attack	Partial onset SGTCS	–	Headache Papilledema	1.N 2. N	SSS Thrombosis	12	Seizure free AED stopped
3	24	M	22	CVT	Attack	Partial onset	–	Headache Papilledema	1. Slow waves 2. N 3.N	SSS Thrombosis	24	Seizure free AED continue Termination plan
4	28	M	25	CVT	Attack	Partial onset SGTCS	–	Headache Papilledema	1. Slow waves 2. N	TS Thrombosis	30	Seizure free AED continue termination plan
5	26	F	25	CVT	Course	Partial onset SE	High Pro Pro: 68 mg/dl Mild Pleocytosis	RHH Papilledema	1. Seizure act 2. L T Sharp w 3.LTSharpw 4. L T Sharp w	TS Thrombosis Venous Infarct	66	Seizure free Recurrence when AED decrease Seizure free with treatment
6	24	M	16	CVT	Before Attack	Myoclonic GTCS	–	Headache	1. Spike wave 2. Spike wave 3. Spike Wave	SSS Thrombosis	55	Rare myocloni AED continue
7	49	M	42	Brain stem lesion	Course	Partial onset	High pro Pro: 89 mg/dl Moderate Pleocytosis	Hemiparesis decrease consciousness	1. Slow waves	Brain Stem lesion	3	Seizure free Died

BD, Behcet disease; NBD, Neuro-Behcet disease; CSF, cerebrospinal fluid; CVT, cerebral sinus thrombosis; SGTCS, secondary generalized tonic clonic seizure; GTCS, generalized tonic clonic seizure; act, activity; SSS, superior sagittal sinus; TS, transverse sinus; EEG, electroencephalography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; HH, hemi-hypoesthesia; AED, antiepileptic drug; JME, juvenile myoclonic epilepsy; Dx, diagnosis; SE, status epilepticus; Pro, protein.

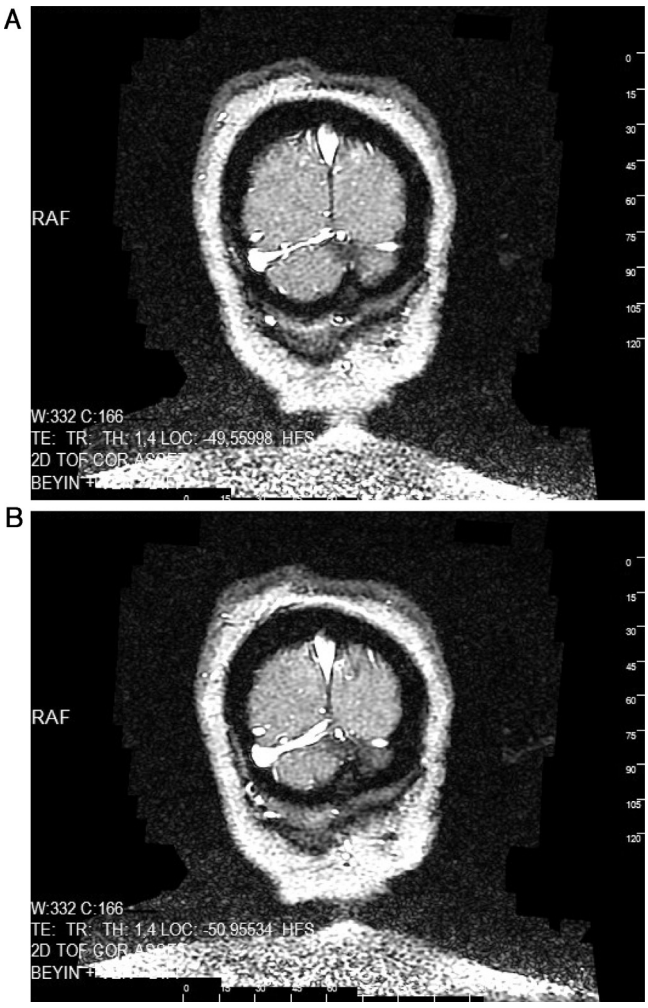

Fig. 1. (A) and (B) Left transverse sinus thrombosis in magnetic resonance venography.

Patient 6. His seizures were started 3 months before the diagnosis of CVT. During 55 months of follow up, rare myoclonic jerks were occurred under the treatment of valproic acid. Multiple spikes and poly-spikes were seen in his EEGs. In the medical history, his grand mother had also epilepsy, however we do not have any information about the type of seizures.

The remaining patient with epileptic seizure (Patient 7) had CNS parenchymal involvement. Cranial magnetic resonance imaging revealed a lesion in brainstem especially mesencephalic region and it ascended to both thalamus. The progression of BD was very aggressive for this patient. Many systemic such as pulmonary system and gastrointestinal system involvement were also seen besides NBD. Complex partial seizures were started one month after the diagnosis of brainstem lesion. CSF examination revealed high protein content and moderate pleocytosis. He was intubated because of pulmonary involvement and died after three months. Levetiracetam was started after two complex seizures and no seizure was observed with this treatment during short follow up period. EEG showed only slow waves.

4. Discussion

In our study, seizures (16.7%) were seen more frequently from previous study. Aykutlu et al. found that 10 (4.48%) of 223 patients with BD had seizures [9]. The larger number of CVT patients might cause the higher ratio in our group. In this study, CVT was diagnosed in six patients whereas brainstem parenchymal lesion was present in only one patient. Seizures were the first presentation of the CVT in four patients. The prognosis of these patients was very good in terms of epileptic seizures and NBD. CVT is one of the major neurological presentations of NBD [15]. The main clinical signs of CVT were headache, seizures, and focal neurological signs, papilledema, and decreased level of consciousness [16,17]. In our patients, four of them had headache and papilledema besides the seizures. Patient with late onset seizures had papilledema and right hemi-hypoesthesia in the acute presentation of the CVT. Patient with seizures before the diagnosis of NBD had only severe headache. Good prognosis was reported for BD patients with CVT like our patients [18]. The antiepileptic treatment was stopped in two patients while we decided to terminate the treatment in other two patients. They did not have any seizure during their follow up. The treatment could not be

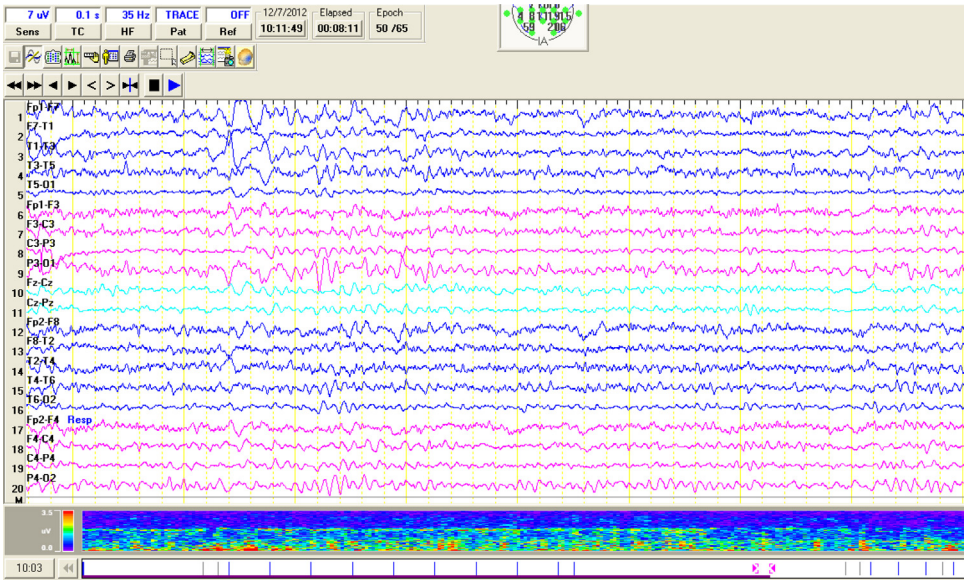

Fig. 2. Left temporal sharp waves.

stopped in patients with venous infarct because of seizure recurrence, so the duration of treatment must be longer in patients with cortical lesions. The remaining patient, who had seizures before the diagnosis of NBD, described myoclonic jerks and GTCS and multiple spikes and poly-spikes were observed in his EEGs. This EEG finding and clinical presentation could be observed both myoclonic epilepsy and frontal lobe epilepsy, so differential diagnosis cannot be done. The treatment was continued because of his rare jerks.

The patients with brainstem lesion had complex partial seizures during the course of NBD. The seizure was begun one month after the diagnosis of NBD. CSF examination showed elevated protein level and pleocytosis. The BD duration was 84 months, however, not only NBD but also systemic presentation of BD had also rapid progression in especially last 4 months. He was died 3 months after the seizure beginning probably due to pulmonary involvement of BD. His seizures were completely controlled by levetiracetam. Previously, NBD has a high rate of mortality about 10% [6]. In another report, four patients were deceased among 10 NBD patients with seizures [9]. According to these studies and our study, brainstem involvement together with seizure occurrence may be predictor of poor prognosis and may cause high mortality rates. New studies should be designed to enlighten this hypothesis.

All patient had EEG examination. Sixteen routine EEG and one sleep EEG was performed to the patients. Two patients had normal EEG in their follow up. EEG revealed slow waves at the beginning (they may be postictal EEG) in other two patients and recurrent EEG for them were also normal. Antiepileptic drug treatment was stopped in two of them with normal EEG and the treatment termination was planned in the other two. They all seizure free during follow up, so normal EEG is a supporting findings of the good prognosis for seizures. EEG of the patient with venous infarct had ictal activity at the admission. Left temporal sharp waves were present in all EEG after the control of status epilepticus. We cannot stop the treatment for epilepsy in this patient because of seizure recurrence. Two routine EEG and one sleep EEG was applied to the patients with seizures before the diagnosis of NBD. All EEG showed us multiple spike and poly-spike waves. Matsumoto found that the EEG changes seemed to be well correlated with the clinical symptoms [19]. We also found the correlation between the seizure prognosis and EEG. Another study described a patient with a progressive NBD whose initial EEG showed periodic lateralized epileptiform discharges (PLEDs) [20]. PLEDs were not observed in EEGs of our cases including the patients with aggressive presentation.

Status epilepticus is very rarely seen in NBD. The case of epilepsia partialis continua and recurrent status epilepticus were reported from Turkey [9,10], previously. In our study, one patient had complex partial status epilepticus seven weeks after the diagnosis of CVT.

The cause of seizures mainly might be due to the increased intracranial pressure rather than the neuro-inflammatory changes. One patient also had cerebral cortical venous infarction and the seizures of this patient mainly due to the lesion. Superior sagittal sinus thrombosis was observed in four patients with (4/6–66.7% versus patients without seizure 4/10–40%), whereas only two patients had transverse sinus thrombosis, one of them had also cortical infarct. Superior sagittal sinus thrombosis ratio was high (4/6–66.6%) in patients with seizures when we compared them patients without seizures (4/10–40%). One of the patients with transverse sinus thrombosis had also cortical infarct and no cortical infarction was detected in patients without seizures. We thought that superior sagittal thrombosis or cortical infarct would be predictor of seizures occurrence because of the high ratio in patients with seizures.

5. Conclusion

CVT seen in BD seems to be the main risk factor for epileptic seizures in patients with NBD. The prognosis is usually good especially in the patients with CVT. Epileptic seizures in patients with brainstem involvement may be an indicator for poor prognosis. Superior sagittal thrombosis or cortical infarct would be predictor of seizures occurrence because of the high ratio in patients with seizures. Therefore multi-centric studies, which were containing large number of patients, are necessary to evaluate association between NBD, localization of CVT and epileptic seizures type and frequency, status epilepticus, EEG, and prognosis.

Conflict of interest

None declared.

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