

# Epileptic Seizures Related to Cerebral Venous Sinus Thrombosis: Clinicoradiological Findings and Cases of Delayed Diagnosis

## Serebral Venöz Sinüs Trombozuna Bağlı Epileptik Nöbetler: Klinik ve Radyolojik Bulgular ve Gecikmiş Tanı Nedenleri

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### Summary

**Objectives:** We aimed to describe clinicoradiological findings and determine some causes of misdiagnosis or delay in diagnosis of patients with epileptic seizures and status epilepticus related to cerebral venous sinus thrombosis.

**Methods:** Nine patients with seizures or status epilepticus associated with cerebral venous sinus thrombosis, admitted to the intensive care unit between November 2012 and November 2013, were included in the study. Full neurological and ophthalmological examinations, electroencephalography, computerized tomography, magnetic resonance imaging and magnetic resonance venography were performed on all of the patients. Also, previous history of neuropsychiatric disorders, initial findings of cerebral venous sinus thrombosis, specialties, where they were initially directed, and treatment interventions were recorded.

**Results:** The main initial clinical symptom was headache in all patients. All patients had a sub-acute progression of disease. Five patients had convulsive, one had non-convulsive status epilepticus. Six patients had presenting seizures (i.e., seizures occurred before confirmation of diagnosis). The superior sagittal sinus was affected in all cases, except in patients 5 and 6. Initial diagnoses in some patients were eclampsia, dissociative disorder, subarachnoid hemorrhage, migraine, and psychotic disorder.

**Conclusion:** Different clinical presentations of cerebral venous sinus thrombosis and the need for differential diagnosis with respect to similar neuropsychiatric diseases often cause the delay of early diagnosis and treatment of cerebral venous sinus thrombosis, and thus lead to the development of epileptic seizures and even status epilepticus.

**Key words:** Cerebral venous sinus thrombosis; diagnosis; seizure.

### Özet

**Amaç:** Çalışmamızda, epileptik nöbet ve status epilepticus gelişen serebral venöz sinüs trombozlu hastaların klinik ve radyolojik özellikleri ile yanlış veya gecikmiş tanı nedenlerini sunmayı amaçladık.

**Gereç ve Yöntem:** Çalışmaya Kasım 2012-Kasım 2013 tarihleri arasında yoğun bakım ünitesinde epileptik nöbet veya status epilepticus ile takip edilen ve serebral venöz tromboz tanısı alan dokuz hasta alındı. Tüm hastaların ayrıntılı nörolojik ve oftalmolojik muayeneleri ve elektroensefalografi, kranial tomografi, manyetik rezonans görüntüleme ve manyetik rezonans venografi yapıldı. Ayrıca daha önceki nöropsikiyatrik hastalık öyküleri, başvuru semptomları, başvurdıkları hekim branşları ve tedavi protokolleri kaydedildi.

**Bulgular:** Tüm hastalarda hastaneye başvuru esnasında en önemli semptom baş ağrısı idi. Tüm hastalar subakut bir progresyon göstermişlerdi. Beş hastada konvulsif ve bir hastada nonkonvulsif status epilepticus tablosu gelişti. Altı hasta nöbet ile başvurmuştu (nöbetler hasta tanı almadan önce oluşmuştu). Beş ve altı numaralı hastalar dışında tüm hastalarda superior sagittal sinüs etkilenmişti. Hastaların ön tanılarından bazıları arasında eklampsi, dissosiyatif bozukluk, subaraknoid hemoraji, migren ve psikiyatrik hastalıklar yer almakta idi.

**Sonuç:** Çok farklı klinik tablolar ile presente olan serebral venöz trombus hastalarının bulguları özellikle psikiyatrik hastalıklar ile benzerlik göstermektedir. Bu nedenle tanı ve tedavide gecikmeler yaşanabilmekte ve bu durum nöbetler ve özellikle status epilepticus gibi ciddi tablolara yol açabilmektedir.

**Anahtar sözcükler:** Serebral venöz sinüs trombozu; tanı; nöbet.

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## Introduction

Cerebral venous sinus thrombosis (CVST) is a neurological emergency characterized by thrombosis of the intracranial venous sinuses and/or cerebral veins, which leads to retention of venous drainage, increase in intracranial pressure and/or venous infarcts.<sup>[1]</sup> CSVT is responsible for about 1% of strokes.<sup>[2]</sup> CSVT has acute, sub-acute and chronic speeds of onset and may present with a wide spectrum of clinical findings. Clinical presentations of CVST range from headache and vomiting to focal neurological signs and loss of consciousness. A frequent feature of CVST is epileptic seizures or even status epilepticus (SE) that usually develops in the early stages of the disease.<sup>[3,4]</sup> The results of previous studies have shown that one third of CVST patients experience focal or generalized epileptic seizures before confirmation of the diagnosis.<sup>[5]</sup> Different clinical presentations and the need for a differential diagnosis from other similar diseases are the usual causes of delay of early diagnosis and treatment of CVST. Thus, delayed diagnosis of CVST might be one cause of the development of refractory seizures of epileptic status, which is a serious emergency condition with high mortality and morbidity.<sup>[6,7]</sup> For these reasons, we focused on presenting epileptic seizures (i.e. seizures that occur before confirmation of a diagnosis of CVST) and, especially, on presenting status epilepticus, and explored some causes of misdiagnosis or delay of diagnosis in patients with cerebral venous sinus thrombosis. We also aimed to describe the clinico-radiological findings of patients with CVST with seizures, who were treated in our intensive care unit (ICU).

## Materials and Methods

Patients admitted to the Kafkas University Medical Faculty NICU between November 2012 and November 2013 were included in this study. In this period, 11 adult patients with CSVT were admitted to the ICU. We selected only 9 patients with presenting and early epileptic seizures.

CVST was diagnosed according to two diagnostic criteria: clinical (seizures or encephalopathy) and radiological (magnetic resonance venography demonstrating absence of flow in venous channels).<sup>[8]</sup> For the exact diagnosis of CVST, we performed full neurological examinations and all three computerized cerebral tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance venography (MRV). CTs were not performed on pregnant women. All pa-

tients underwent a wide hematological, biochemical and, if necessary, genetic work-up, aimed at investigating predisposing factors for CVST and seizures.

We recorded the main clinico-radiological findings and treatment interventions, and calculated the mean duration of treatment in the NICU, mean time from the onset of symptoms to development of epileptic seizures and the mean time from the onset of seizures to confirmation of the final diagnosis in patients with presenting seizures. Also, patients' neurological status on admission and discharge were assessed with the modified Rankin Scale (mRS).<sup>[9]</sup>

We excluded patients with a previous history of epilepsy and patients with status epilepticus provoked by metabolic derangement, alcohol or drug intoxication or withdrawal, and those who used medications with a relative risk for developing epilepsy (such as some selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors and sympathomimetics). Subjects under 18 years of age, and patients with subarachnoid, subdural, and epidural hemorrhages were also excluded.

## Definitions

**Epileptic status:** The definition of generalized SE refers to >30 minutes of a single epileptic seizure or 2 or more discrete seizures between which there is incomplete recovery of consciousness. Status epilepticus was subgrouped as convulsive and nonconvulsive according to clinical symptoms and electroencephalography (EEG).<sup>[10,11]</sup>

**Convulsive SE** is defined as tonic-clonic (generalized convulsive status epilepticus (GCSE)) and myoclonic.

**Nonconvulsive SE (NCSE)** is defined as impaired consciousness lasting at least 30 min with persistent or continuous epileptiform abnormality in the EEG.<sup>[12]</sup> Nonconvulsive status epilepticus (NCSE) encompasses all forms of SE in which the motor manifestations are absent or minimal, and as such can be difficult to diagnose without an EEG.

**Presenting seizures** have been defined as occurring before the confirmation of a diagnosis of CVST.<sup>[13,14]</sup>

**Early seizures** have been defined as those first occurring within 2 weeks after stroke.<sup>[13,14]</sup>

## Results

In the period between November 2012 and November 2013, a total of 11 patients with a diagnosis of CVST were admitted to the NICU. We evaluated nine patients (81.8%) who had epileptic seizures. Eight of those were female and 1 male with a mean age 36.1 (min 25-max 44) years. Six (54.5%) had SE, one of which had NCSE. The other 5 patients had GCSE. Todd's paresis was present in a single patient (patient 2). The demographic, clinical, and radiological characteristics of patients are summarized in Table 1.

The course of the CVST in all patients was sub-acute (i.e. the symptoms developed between 48 h and 30 days).<sup>[15]</sup> The mean hospitalization period in the NICU was 7.6 days (min 4-max 18 days). None of the patients died during treatment in the NICU or in hospital.

All patients received heparin or low molecular weight heparin and later warfarin, despite the presence of hemorrhagic infarct in two of the patients. Raised intracranial pressure was treated by intravenous mannitol, and sometimes hyper-

tonic NaCl solutions. Epileptic seizures were managed with intravenous diazepam, phenytoin sodium and valproic acid according to the guidelines.<sup>[16]</sup> Patient 3 underwent a caesarean section under general anesthesia and was intubated for 4 days because of insufficient spontaneous breathing after cardiopulmonary arrest at the time of admission. During the intubation period this patient received propofol and midazolam infusions to control her epileptic seizures.

The superior sagittal sinus (SSS) was affected in all cases, except patients 5 and 6. The both transverse and sigmoid sinuses were affected in 5 and 6 cases, respectively. Sample radiological imagings of patients are presented in Figure 1.

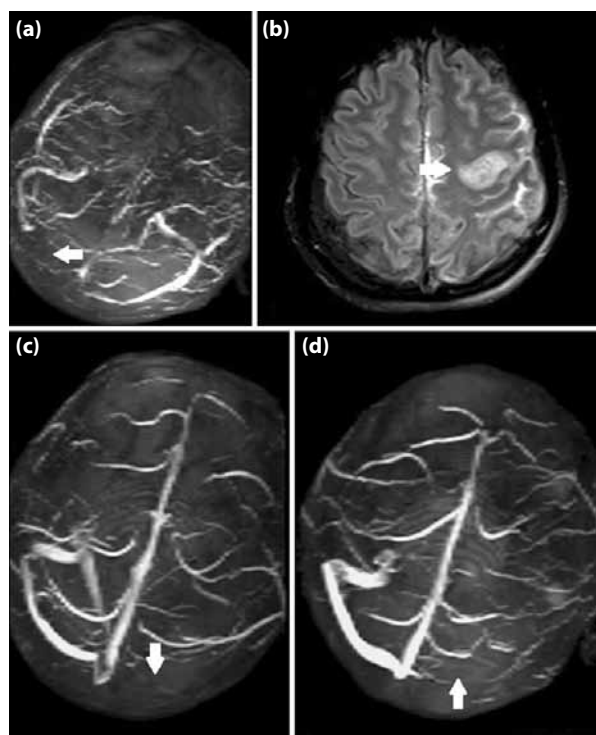
EEG (10-20 system) was performed on all of the patients for final confirmation of diagnosis and follow-up of the course of the disease. Sample EEG sequences of patient 4 with NCSE are shown in Figure 2.

All patients with initial complaints as headache, vomiting and psychotic symptoms, were initially admitted to outpatient clinics or emergency units of secondary medical

**Table 1.** Demographic, clinoradiological findings and initial diagnosis of patients

Patients	1	2	3	4	5	6	7	8	9
Age/gender	42/F	29/M	25/F	41/F	39/F	37/F	31/F	37/F	44/F
Initial symptoms									
Headache	+	+	+	-/+	+	+	+	+	+
Vomiting	-	+	-	-	+	-	+	+	+
Encephalo-pathy	+	-	+	+	-	+	-	-	-
Papilledema	-	-	+	-	+	+	-	-	-
Hemiparesia	+/-	+/-	-	-	-	+	-	-	-
Site of thrombosis	SSS	SSS	SSS	SSS	TS	SS	SSS	SSS	SSS
	TS	TS		TS	SS	TS	SS	TS	SS
Seizures									
Presenting		+	+	+	+	+		+	
Early	+						+		+
SE		+	+	+	+	+		+	
Initial diagnosis	DD	Migr	Eclmp	Psyc. disord.	CNS met.	Stroke	Migr	SAH	Migr
Predispos. factors	DH	Hom	Preg, HT, MTHFR	OCS, Smok.	CA	OCS	Puerp	OCS	OCS
mRS in admission	5	4	5	5	4	4	4	5	4
mRS in discharge	0	0	0	0	0	0	0	0	0

CA: Gastric cancer; CNS: Met-central nervous system metastasis; Delir: Delirium; DD: Dissociative (conversion) disorder; DH: Dehidratation; Eclmp: Eclampsia; Hom: Hyperhomocysteinemia; HT: Arterial hypertension; Migr: Migraine; mRS: Modified Rankin Scale; MTHFR: Methylene-tetrahydrofolate reductase gene mutation; OCS: Oral contraception; Preg: Pregnancy; Puerp: Puerperium; Psyc. Disord.: Psychotic disorder; SAH: Subarachnoid hemorrhage; SE: Status epilepticus; SS: Sigmoid sinus; Smok.: Smoking; SSS: Superior sagittal sinus; TS: Transvers sinus; +: Present; -: Absent.



**Figure 1.** Sample MRI of patients with cerebral venous sinus thrombosis: **(a)** thrombosis in superior sagittal and right transverse sinus in patient 2; **(b)** venous hemorrhagic infarct in left parietal lobe in patient 3; **(c)** left transverse and sigmoid sinuses thrombosis in patient 5; **(d)** occlusion in left sigmoid and transverse sinuses in patient 6.

centers. Patients 5 and 8 were previously referred to a neurosurgeon (with a diagnosis of intracerebral metastasis and subarachnoid hemorrhage, respectively), patient 4 to a psy-

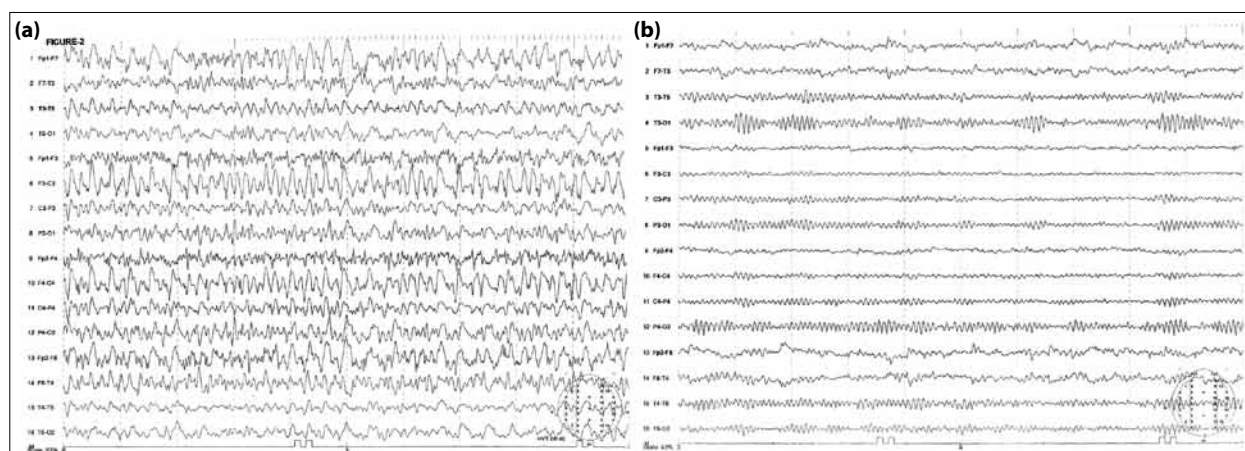
chiatrist (psychotic disorder) and patient 3 to a gynecologist (eclampsia). The mean time between the onset of first symptoms (usually headache and vomiting) and development of seizures was 3.1 (min 1-max 5) days. The mean time between the onset of seizures to confirmation of diagnosis was 5.2 hours.

## Discussion

One of the emergency conditions in CVST is early epileptic seizures (and even SE), which develop in 26.6%-44.3% of cases of CVST.<sup>[4,17-19]</sup> Patients with CVST are significantly more at risk to develop a seizure than patients with hemorrhage or ischemic stroke.<sup>[17]</sup> Status epilepticus has a poor prognosis and is one of the main causes of early death in CVST.<sup>[20]</sup>

As we know, only a few studies have investigated in detail the frequency of seizures and clinico-radiological findings of CVST patients with seizures. Ferro et al., in their study of 91 registered patients, reported that 34% of them had early symptomatic seizures. Especially, patients with motor and sensory deficits and with focal edema, ischemic infarcts or hemorrhages had early symptomatic seizures. Statistical analyses have shown that a parenchymal lesion on admission CT/MR and sensory defects were found to be significant risk factors for early symptomatic seizures. While seizures can be a cause of sudden death, they were not related to functional prognosis on the last follow-up.<sup>[3]</sup>

A more recent prospective study of demographic, clinical and radiological characteristics of 194 consecutive patients with acute CVST analyzed the frequency of ES and in-hos-



**Figure 2.** (a, b) Sample EEG traces in patient 4 with nonconvulsive status epilepticus before and after administration of intravenous diazepam.

pital mortality. Early symptomatic seizures were found in 44.3% of patients. Motor deficit, intracranial hemorrhage and cortical venous thrombosis were independent predictors of early epileptic seizures. SE occurred in 11 patients (12.8%). Patients with focal motor deficits, cortical venous thrombosis and intracranial hemorrhage carried the highest risk for SE. Four of the 11 patients with SE died. Amongst patients with epileptic seizures, mortality rate was three times higher in those with status than in those without (36.4% and 12%, respectively). The authors suggested that SE was an important source of morbidity and early mortality in patients with CVST.<sup>[4]</sup>

Another multicenter, prospective, observational study has reported that 245 of 624 (39.3%) patients with CVST experienced presenting seizures, and 43 (6.9%) patients had early seizures. Supratentorial lesion, sagittal sinus thrombosis and puerperal CVST were associated with presenting seizures, whereas supratentorial lesion and presenting seizures predicted early seizures.<sup>[5]</sup>

A further study performed on 94 patients by Davoudi et al. found that 19.1% of patients experienced presenting seizures and 21.3 % of patients had early seizures in the 2. week after confirmation of the CVST diagnosis.<sup>[19]</sup>

In the study of Kalita et al. 46.7% of patients with CVST had presenting seizures and 4.4% had early seizures, which were independently related to supratentorial lesion.<sup>[21]</sup>

The results of all these studies support our findings: all of the patients with seizures had supratentorial lesions (mainly with a hemorrhagic component), 2 patients had motor weakness, and 2 patients were pregnant. While SE was associated with relatively high mortality and morbidity in the studies of Masuhr et al. and Ferro et al., none of our patients lost their lives and they were discharged without any significant neurological deficits, despite the fact they were admitted to the NICU in serious conditions.<sup>[3,4,20]</sup>

All of the mentioned studies investigated the main clinico-radiological findings that predicted seizures. In addition to these studies, a significant finding in our study is that the diagnosis of CSVT was delayed in many of the patients, which, in turn, led to the development of seizures and SE and resulted with the patients being admitted to the ICU. Depending on our present experience, we consider that

some factors may cause a delay or even a misdiagnosis of CVST in the early stage. First, it is known that headache is the most common symptom and is present in about 90% of patients with CVST.<sup>[22,23]</sup> In particular, a migrainous type of headache has been described in some patients.<sup>[24]</sup> An isolated headache without focal neurological signs or papilledema was reported in approximately 25% of CVST patients and presents a significant diagnostic handicap.<sup>[25]</sup> As a confirmation of these results, headache (sometimes migrainous) was a gross and isolated initial symptom in many of our patients, and partly interfered with the true diagnosis. Second, the initial CTs were in the normal range for all of the patients. It should be noted that standard unenhanced CT imaging is normal in 30% of patients with CVST which was also supported by our results.<sup>[26]</sup> Also, most of our patients were directed to such specialties as psychiatry, neurosurgery or gynecology, where confirmation of a diagnosis of CSVT is most often impossible. Finally, insignificant or uncharacteristic clinical features at the stage of presentation and sub-acute progression of the disease could also have caused the delay. As we know, up to 50% of cases of CSVT present with sub-acute progression between 48 h and 30 days; it also creates difficulties in diagnosis. A relatively rare type of stroke, the young age of patients, absence of significant risk factors for stroke, previous history of migrainous type of headache-all of these factors hinder the diagnosis of CVST. On the other hand, occurrence of seizures in combination with other clinico-radiological findings accelerated the confirmation of the final diagnosis. Yet, we cannot extend our observation to a wide population of patients due to the fact that we have included only patients who were admitted to the NICU, thus causing a selection bias towards more severe cases.

In summary, CVST may have diverse clinical presentations and it might be confused with other neuropsychiatric diseases such as different types of stroke, metabolic, toxic and other encephalopathies or psychotic disturbances. Therefore, the CVST might be misdiagnosed and early treatment of the patient might be delayed. We believe that clinicians, who encounter a young patient with seizures without a previous history of epilepsy, or acute psychotic impairment without a previous psychiatric history, should take into account the possibility of CVST.

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