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ORIGINAL ARTICLE

Headache as the sole presenting symptom of cerebral venous sinuses thrombosis: Subgroup analysis of data from the VENOST study

Tek semptomu baş ağrısı olan serebral venöz sinüs trombozu: VENOST çalışmasından elde edilen verilerin alt grup analizi

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Summary

Objectives: Headache is the most common complaint in cerebral venous sinus thrombosis (CVST) and it may sometimes be the only symptom in these patients. This retrospective and prospective study was an investigation of any differences in terms of clinical risk factors, radiological findings, or prognosis in patients with CVST who presented with isolated headache (IH) and cases with other concomitant findings (non-isolated headache [NIH]).

Methods: A total of 1144 patients from a multicenter study of cerebral venous sinus thrombosis (VENOST study) were enrolled in this research. The demographic, biochemical, clinical, and radiological aspects of 287 IH cases and 857 NIH cases were compared.

Results: There were twice as many women as men in the study group. In the IH group, when gender distribution was evaluated by age group, no statistically significant difference was found. The onset of headache was frequently subacute and chronic in the IH group, but an acute onset was more common in the NIH group. Other neurological findings were observed in 29% of the IH group during follow-up. A previous history of deep, cerebral, or other venous thromboembolism was less common in the IH group than in the NIH group. Transverse sinus involvement was greater in the IH group, whereas sagittal sinus involvement was greater in the NIH group. The presence of a plasminogen activator inhibitor (PAI) mutation was significantly greater in the IH group.

Conclusion: IH and CVST should be kept in mind if a patient has subacute or chronic headache. PAI, which has an important role in thrombolytic events, may be a risk factor in CVST. Detailed hematological investigations should be considered. Additional studies are needed.

Keywords: Cerebral venous sinus thrombosis; cerebrovascular disease; headache.

Özet

Amaç: Baş ağrısı serebral venöz sinüs trombozunda (SVST) en sık görülen şikayettir ve bazen CVST ile başvuran hastalarda görülen tek semptom olabilir. Bu retrospektif ve prospektif çalışmada, izole başağrısı (IB) ile başvuran SVST olgularında ve baş ağrısı ile ilişkili diğer bulguları olan (izole olmayan başağrısı-İOBA) olgularda klinik risk faktörleri, radyoloji ve prognoz açısından herhangi bir farklılık olup olmadığını araştırdık.

Gereç ve Yöntem: Serebral venöz sinüs trombozu (VENOST) çok merkezli çalışmasından 1144 hasta çalışmamıza alındı. Tüm demografik, biyokimyasal, klinik ve radyolojik yönler 287 IBA vakası ve 857 İOBA vakası için karşılaştırılmıştır.

Bulgular: Toplam grup içinde kadın oranı iki kat daha yüksekti. İBA grubunda cinsiyet dağılımını yaş gruplarına göre değerlendirildiğinde istatistiksel olarak anlamlı bir fark bulunmadı. İBA grubunda, baş ağrısının başlangıcı sıklıkla subakut ve kronikti, ancak akut başlangıç, İOBA grubunda daha yaygındı. İBA grubunda% 29'luk takip sırasında diğer nörolojik bulgular eklenmiştir. Daha önce serebral, derin ve diğer venöz tromboembolizm öyküsü İBA grubunda İOBA grubuna göre daha azdı. Transvers sinüs tutulumu İBA grubunda daha yüksek iken sagital sinüs tutulumu İOBA grubunda daha fazlaydı. Plazminojen aktivatör inhibitörü (PAI) mutasyonu IBA grubunda anlamlı olarak daha yüksekti.

Sonuç: Hastaların subakut veya kronik baş ağrısı varsa SVST tanısı için IBA akılda tutulmalıdır. Trombolitik olaylar için önemli bir role sahip olan PAI, SVST'da bir risk faktörü olabilir, bu nedenle ayrıntılı hematolojik araştırmalar düşünülmelidir. Daha ileri çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Serebrovasküler hastalık; baş ağrısı; serebral venöz sinüs trombozu.

Introduction

Patients may present with various symptoms as a result of cerebral venous sinus thrombosis (CVST) of dural venous sinuses and deep and superficial cerebral veins thrombosis.[1] CVST can mimic other diseases with different clinical manifestations ranging from headache to coma. CVST may present with a single finding or may be seen as a syndrome consisting of many findings. Clinically unclear process may complicate the diagnosis of CVST.[2,3]

In many studies, it has been reported that headache is seen in in more than 80% of the cases is the most common first symptom. Headache in CVST is not typical and other neurological symptoms such as seizures, papilloedema, focal deficits, cranial nerve paralysis or impaired consciousness can be added to headache.[4]

The mechanism of headache in CVST is not known when there is not intracranial hypertension, subarachnoid haemorrhage (SAH), meningitis or intracranial lesion.

There is a possibility that nerve fibers are affected in the obstructed sinuses. In addition, it is possible to have contrast involvement around the clot, which is known as the 'empty delta sign' which is a dilatation of the vessels as a result of local inflammation of the sinuses.[4,5]

Rarely, headache in CVST may not be associated with any clinical findings. However brain computed tomography (CT) scanning and/or cerebrospinal fluid (CSF) examination usually reveal the conditions such as SAH, intracerebral infarction or haemorrhage that can be the cause of headache of CVST. In the absence of such conditions in CVST, it is rare to have only headache complaints.[6–8]

In this study, we presented the characteristics of 1144 patients in whom headache was the only clini-

cal presentation of CVST in the absence of other aetiological factors which are assessed by imaging tests. Also the aim of this study was to investigate the clues for the diagnosis of CVST only in patients with headache.

Material and Methods

Patient selection

The study design of cerebral venous thrombosis (VENOST), an international multicentre observational study involving 1144 patients who were retrospectively diagnosed with CVST between June 2000 and June 2015, was described in detail.[9] The study was approved by the ethics committee of the centers (no: 83045809/604/02-12333).

This study includes all members of the VENOST group. In VENOST, CVST was diagnosed based on the patient's clinical findings and the presence of thrombosis in the cerebral venous sinuses detected using brain computed tomography (CT), brain magnetic resonance imaging (MRI), MR venography (MRV) and/or digital subtraction angiography (DSA).

The patients were divided into two groups according to headaches such as; the cases with CVST that comes with only headache (isolated headache-IH) and cases with other findings in addition to headache (non-isolated headache-NIH).

Both groups were compared according to their initial clinical findings on admission, etiologic factors, imaging findings and prognostic factors.

Research on thrombotic risk factors was performed in 63.7% of the participating centers.[10] Methylenetetrahydrofolate reductase (MTHFR), prothrombin mutation, plasminogen activator inhibitör (PAI) mutation, Factor V Leiden mutation test was performed in 729 patients; Antiphospholipid Ab, hyperhomocysteinemia, hyperfibrinogenemia, antithrombin III and protein C/S deficiency, activated protein C resistance, antinuclear antibody (ANA) positivity, thrombocytosis, anticardiolipin Ab were measured in 941 patients.[9]

Etiological risk factors such as infections, systemic inflammatory diseases, rheumatologic or connective tissue diseases, malignancy, hematologic diseases and the other causes were also recorded.

On admission, the duration of symptoms was accepted as acute if the duration is less than 48 hours, subacute between 48 hours and 1 month and chronic if the duration of symptoms was more than 1 month.

Follow-up examination results were classified according to the modified Rankin Scale (mRS). MRS score was classified as 0–1 independent (favorable outcome), mRS score 2 minimum disability and mRS score 3–6 dependent or dead (poor outcome).

The visits of the cases were recorded 1, 3, 6 and 12 months after the initial diagnosis of CVST.

Results

Mean age and female/male ratio of IH group (n: 287, 25.1%) were 40.1±13.3 years and 185/102; NIH group (n: 857, 74.9%) were 40.04±13.8 years and 592/265 respectively. Statistically meaningful age difference was not detected between IH and NIH groups (Table 1).

In the IH group, when evaluated the gender distribution by age groups, there was no statistically significant difference (p=0.115). In the NIH group, the ratio of female/male between the ages of 18–36 was found equal (female/male ratio: 46/46%), the ratio of female in the 37–50 year-old group was higher (female/male ratio: 37/26%); in the age group >50 years and the ratio of male was significantly higher (female/male oranı: 17/28%) (p<0.001).

In the IH group, onset of headache was frequently subacute and chronic, but an acute onset was more common in the NIH group (Table 1).

Detailed radiological evaluation (MRI and MRV) was performed in 92% of the IH group and 88.1% of the NIH group. Only MR, MRV, CT + MRV were performed in other cases (Table 1).

It was seen that 10 (29%) patients in IH group had additional neurological findings including nausea, vomiting, epileptic seizures, visual field defect, focal neurological deficit, altered consciousness and cranial nerve palsies during follow-up. In the NIH group neurological findings were existed at the beginning

In IH group there was no difference according to existence of parenchymal lesions. In the NIH group,

parenchymal lesions as infarction, hemorrhage and hemorrhagic transformation were seen more often than the other group (Table 1).

A previous cerebral, deep and other venous thromboembolism history was less common in IH group than the NIH group (Table 2).

Transverse sinus involvement was higher in IH group, whereas sagittal sinus involvement was higher in NIH group.

The prognosis of IH group was better than NIH group according to mRS.

When the hematological parameters were examined, plasminogen activator inhibitor (PAI) mutation was significantly higher in IH group (Table 2).

Discussion

CVST is a complicated process because it may present with different clinical situations.[11] Rarely CVST may occur with headache alone and there may not always be an additional finding so that CVST may usually be thought to be secondary headache disorders.[12] Headache was reported to be the most common symptom in 92% of CVST cases in a study. In addition, approximately one-third of patients reported only sole manifestation.[13] In our study, headache was the only onset symptom in one third of the patients. Our results were consistent with the previous studies. In CVST, 84% of headaches begin as acute to subacute, while 20% had a chronic onset.[7,14,15] In our IH group, 33% of CVST cases had chronic type headache.

CVST diagnosis may be made earlier in the patient who comes to the hospital with changes in consciousness, mental disorders and seizures,[7] but care should be taken to avoid misdiagnosis by taking into account the unfamiliar initial pattern in CVST patients with chronic headache. The possibility of CVST should be considered if a chronic intermittent headache worsens or if a new onset chronic headache develops.[14,15] For this reason, patients with subacute or chronic headache should still be examined and venous thrombosis should also be kept in mind. Therefore, detailed radiological evaluation helps in diagnosis and affects treatment positively. Because of this CT with or without contrast may not be sensitive enough to rule out CVST in patients with headache. The remarkable use of MRI and especially the increase in the use of MRV has made this diagnosis easier.[11] In previous studies, it is shown that MRI combine with MRV are current diagnostic modality of choice and are the best imaging technique for diagnosis of CVST in patients with unclear findings on CT.[16,17] DSA is the more effective for early diagnosis of dural sinüs lesions but the American Heart and Stroke Association recommend MRI and MRV as a preferred tests for the diagnosis of dural sinus lesions.[18] In our study, 92.3% patients underwent detailed radiological work-ups, including MRI and MRV to put the diagnosis easily.

Patients with CVST may present with variable neurological findings, but usually epileptic seizures, focal neurological deficits and encephalopathy are more common. In a study, focal or generalised seizures occur in 30–50%, papilloedema in 30–60% of CVST patients approximately 10% of patients are comatose at the time of diagnosis.[7,9,19] In our study, epileptic seizures, visual field defects, focal neurological deficits were more common in the NIH group and altered consciousness was found to be 24% of patients.

CVST is usually more common in women than men. In a study it is analyzed that 75% of patients were women.[20] It is seen more often in middle-aged women. In our study when all 1144 patients were evaluated in terms of gender, women were more in the group. Also, most of them were in the middle-aged group.

The cerebral venous system consists of superficial and a deep parts. The superior sagittal and transverse sinuses form the superficial cerebral venous system. Lateral sinus, straight sinus and sigmoid sinus are parts of deeper system.[21] The transverse and superior sagittal sinuses are commonly affected sinuses in CVST.[7] Transverse sinus is the most commonly affected sinus in 77% of cases in a study.[16] In our study, the most effected sinus was transverse sinus in both groups similar to the other studies. However sagittal sinus involvement was higher in NIH group than IH group.

There may be various factors in the etiology of CVST. Genetic and prothrombotic disorders may be among

Table 1. Compared data of demographical and clinical aspects of both groups

	Non-isolated headache (NIH)		Isolated headache (IH)		p
	n=857	75%	n=287	25%	
Age (years)	40.04±13.82		40.15±13.39		0.911
18–36 (years)	397	46.3	136	47.4	
37–50	292	34.1	88	30.7	0.499
>51	168	19.6	63	22	
Gender					
Female	592	69.1	185	64.5	0.147
Male	265	30.9	102	35.5	
Mode of onset					
Acute	442	52.5[a]	88[b]	31	
Subacute	280	33.3[a]	103[a]	36.3	<0.001
Chronic	120	14.3[a]	93[b]	32.7	
Clinical symptoms and signs					
Headache	710	82.8	287	100	<0.001
Nausea and vomiting	317	37	0	0	<0.001
Epileptic seizures	270	31.5	1	0.3	<0.001
Visual field defect	298	34.8	5	1.7	<0.001
Focal neurological deficit	207	24.2	1	0.3	<0.001
Altered consciousness	203	23.7	1	0.3	<0.001
Cranial nerve palsies	126	14.7	2	0.7	<0.001
Radiological work-up					
Cranial MRI	50	5.9	10	3.5	
Cranial MRV	31	3.6	10	3.5	0.115
Cranial MRI+MRV	752	88.1	263	92.3	
Cranial CT+ MRV	21	2.5	2	0.7	
Number of sinuses involved					
1 sinus	401	46.8	150	52.3	
2 sinuses	302	35.2	85	29.6	0.185
3 sinuses	125	14.6	46	16	
4 sinuses	29	3.4	6	2.1	
Involved sinuses					
Isolated transverse sinuses	197	23	95	33.1	0.001
Isolated sagittal sinuses	134	15.6	34	11.8	0.116
Isolated sigmoid sinuses	26	3	11	3.8	0.508
Isolated cortical veins	18	2.1	6	2.1	0.992
Isolated Juguler sinuses	12	1.4	4	1.4	0.994
Isolated cavernous sinuses	9	1.1	0	0	0.122
Transverse sinuses	616	71.9	224	78	0.041
Sigmoid sinuses	334	39	121	42.2	0.340
Sagittal sinuses	369	43.1	76	26.5	<0.001
Internal juguler vein	131	15.3	47	16.4	0.659
Cortical veins	32	3.7	10	3.5	0.846
Cavernous sinuses	15	1.8	4	1.4	0.796
Parenchymal involvement					
No lesion	456	53.2[a]	229[b]	79.8	
Infarction	185	21.6[a]	33[b]	11.5	<0.001
Hemorrhagic infarction	180	21[a]	18[b]	6.3	
Intracerebral hemorrhage	36	4.2[a]	7[a]	2.4	

MRI: Magnetic resonanace imaging; MRV: Magnetic resonance venography; CT: Computed tomography. One-way Anova test: Comparison of a and b: p≤0.05; comparison of a and a: p>0.05.

Table 2. Etiological factors and outcome according to isolated headache and headache with other etiological factors

	Isolated headache (-)		Isolated headache (+)		p
	n=857	75%	n=287	25%	
Infections					
Paracranial (focal)	53	6.2	17	5.9	0.918
Systemic	18	2.1	5	1.7	
History of VTE					
Cerebral	24	2.8[a]	2	0.7[b]	0.045
Deep venous thrombosis	35	4.1[a]	6	2.1[a]	0.712
Other	7	0.8[a]	1	0.3[a]	0.075
Malignancy	43	5.0	16	5.6	
Family history VTE	11	1.3	0	0	0.168
MTHFR mutation					
Heterozygote	28	5	9	5.3	0.254
Homozygote	30	5.4	16	9.4	0.802
Hyperhomocysteinemia	31	4.3	14	6.2	0.133
Prothrombin mutation	15	2.7	4	2.3	0.599
Protein C/S deficiency	40	5.6	7	3.1	0.765
Factor V leiden mutation	27	4.8	10	5.8	0.692
Thrombocytosis	8	1.1	2	0.9	0.634
Polisitemia vera	6	0.8	1	0.4	<0.001
Anticardiolipin Ab	4	0.6	2	0.9	0.345
PAI mutation	2	0.4	8	4.7	0.583
Antithrombin III deficiency	5	0.7	0	0	0.744
Hyperfibrinogenemia	3	0.4	0	0	0.819
Antiphospholipid Ab	9	1.3	2	0.9	
Activated protein C resistance	11	1.5	3	1.3	0.291
High ANA titers	18	2.5	3	1.3	0.11
Behçet disease	74	8.8	34	12.8	0.402
SLE	12	1.4	3	1.1	
1st month					
0–1	569	73.6[a]	218	94.4[b]	
2	110	14.2[a]	7	3[b]	<0.001
≥3	94	12.2[a]	6	2.6[b]	
3rd month					
0–1	562	86.3[a]	202	97.1[b]	
2	51	7.8[a]	3	1.4[b]	<0.001
≥3	38	5.8[a]	3	1.4[b]	
6th month					
0–1	526	89.5[a]	186	97.9[b]	
2	36	6.1[a]	1	0.5[b]	0.001
≥3	26	4.4[a]	3	1.6[a]	
12th month					
0–1	481	91.3[a]	162	98.8[b]	
2	22	4.2[a]	0	0[b]	0.004
≥3	24	4.6[a]	2	1.2[a]	

ANA: Anti nuclear antibody; MTHFR: Methylenetetrahydrofolate reductase; PAI: Plasminogen activator inhibitor; VTE: Venous thromboembolism; SLE: Systemic Lupus Erytematosus. One-way Anova test: Comparison of a and b: p≤0.05; comparison of a and a: p>0.05.

the causes of CVST.[22] In a study, after a detailed examination of patients with cerebral venous thrombosis, 20–35% remains idiopathic.[23] In our study, 44% of the IH group and 53% of the NIH group had no cause of thrombosis. It is shown that 85% of affected patients have at least one risk factor. Among the affected patients, 34% had a prothrombotic condition and 22% had genetic predisposition to the disease.[6] Common hereditary factors are deficiency of antithrombin III, protein C or protein S, activated protein C resistance and prothrombin 20211A mutation.[24] Rare defects include heparin cofactor II, plasminogen or tissue plasminogen activator deficiency, PAI-1 and dysfibrinogenemia.[25] In our study, 37% in the IH group and 42% in the NIH group had prothrombotic conditions. Also, Behçet's disease was the most common cause of prothrombotic disease in both groups.[10] As an interesting finding, the PAI mutation was significantly higher in the IH group. PAI is mainly important in regulating the fibrinolytic system. PAI-1 deficiency can cause abnormal bleeding in humans. Excessive release of PAI-1 may disrupt the normal fibrin formation mechanism in the vessel wall, leading to excessive accumulation of fibrin, resulting in thrombotic events.[22,26] PAI-1 genotype polymorphism expresses PAI-1 at a higher rate and has a higher risk of deep vein thrombosis.[27] In our study, we found that the PAI mutation in IH group was significantly higher than in the other group, but it should be supported by further studies.

It is reported that the outcomes of CVST were positive in 92% of the patients and the mortality rate was reported as 5.4%.[28] Causes of poor prognosis include systemic or central nervous system infections and treatment inadequacies.[29]

In our patients, the prognosis was good in both groups but it was better in the IH group.

Conclusion

CVST should be remembered in patients with only headache symptom, even if headache is subacute or chronic type. Therefore, MRI and MRV should be added to detailed radiological examinations. PAI, which has an important role for thrombolytic events, may be a risk factor in CVST. PAI mutation should be kept in mind in the evaluation for prothrombotic agents. Further studies are needed.

Ethics Committee Approval: The İstanbul University, Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 06.05.2014, number: 83045809/604/02-12333).

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