Original Article

Factors Influencing the Incidence of Papilledema in Patients with Cerebral Venous Thrombosis

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Abstract

Background: Cerebral venous thrombosis (CVT) is an uncommon cerebrovascular disease with a wide spectrum of symptoms and severity. This study analyzes the factors influencing the incidence of papilledema in patients with cerebral venous thrombosis. **Materials and Methods:** In this research 65 patients with CVT were examined between 2011 and 2013, and the patients were followed up one, three, six, and twelve months after the initial diagnosis. They were separated into two groups according to presence or absence of papilledema. We analyzed the frequency of symptoms and risk factors of cerebral venous thrombosis and the intensity of papilledema as time passed, as also the frequency of the involved sinus, in two groups of patients with and without papilledema. **Results:** This study showed that the most common symptom was headache, with a frequency of 92.3% and the least common symptoms were ataxia and quadriparesis, with a frequency of 1.5%. The most common risk factors were high waist circumference (WC) and oral contraceptive pil (OCP) use, and also in patients with papilledema the intensity is reduced as time passes. **Conclusion:** This investigation showed that there was no significant relation between the frequency of risk factors and symptoms and intensity of papilledema as time passed in the two groups. The results showed that the most common sinuses involved in patients with papilledema were sagittal and lateral sinuses, which included 66.7%, and the most common sinus involved in patients without papilledema, which was the lateral sinus that included 40%.

Keywords: *Cerebral venous thrombosis, papilledema, sinus*

Introduction

Cerebral venous thrombosis (CVT) is an uncommon cerebrovascular disease with a wide spectrum of symptoms and severity. The disease can be acute, subacute, or chronic.[1] It affects about five in one million and women are affected three times more than men, usually including young people.[2,3] The disease is observed in 0.5 to 1% of all cases of stroke.[4] The most common symptoms are headache (70 to 80%), weakness (40 to 54%), hemiparesis (40%), seizures (30%), and papilledema (20 to 30%).[4]

Clinical manifestations of the disease depend on such factors as thrombosis location, age, and the presence or absence of simultaneous brain lesions.[5] The most important risk factors of the disease may include coagulation disorders, concurrent cancer, drug use (especially oral contraceptive drugs).[6,7] In a study conducted in 2008 by Wasay *et al.*, the disease was detected in 57% of 182 patients with cerebral venous thrombosis, and in 43%, the disease was idiopathic.[8]

Disease manifestations depend on many factors, one of which is the affected area of the brain. In the local cerebral involvement of the brain, hemiparesis and aphasia are considered as the most common symptoms.[9] Another factor causing the manifestation of the symptoms is venous sinus involvement. When the lateral sinus is involved, frequent manifestations of the disease include background disease symptoms, such as, fever, natural symptoms, and discharge from the ear, while in the case of superior sagittal sinus involvement, symptoms such as increased intracranial pressure and papilledema are considered among the most common symptoms.[10,11] One of the important symptoms of papilledema is vision loss.[12] Magnetic resonance imaging (MRI) or computed tomography scan (CTS) are the first choice for the diagnosis for CVT.[7]

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In 25% of the CVT patients the only symptom is headache and no papilledema is seen.[13,14]

Papilledema is one of the causes of cerebral venous thrombosis and is a condition where the optic nerves become inflamed because of the skull pressing down on them. The most important causes of papilledema can be brain tumors, cerebral edema, meningitis, and cerebral venous thrombosis. However, in some cases there is no known cause for its occurrence. On the other side, in Iran, no study has yet been performed to determine the risk factors. Considering this fact that at least a quarter of patients with cerebral venous thrombosis may have no obvious signs such as papilledema, it makes it difficult to detect CVT. The present study was performed to determine factors affecting the incidence of papilledema in patients with cerebral venous thrombosis.

Materials and Methods

This research is a descriptive–analytical study performed between 2011 and 2013, at Al-Zahra Medical Center in Isfahan, Iran. The population included patients with CVT, diagnosed between 2011 and 2013, and admitted to the center. The inclusion criteria were, the incidence of CVT and the patients' participation agreement to contribute to the study at identified periods.

The sample size required for the study was estimated using the formula for prevalence studies, taking into account the 95% confidence level, the incidence of papilledema in patients with CVT, which was estimated at about 20% in other studies,[5] and accepting a 15% error rate for 30 individuals.

The method started with the initial diagnosis. The patients were examined by ophthalmoscopy and were evaluated for the presence or absence and severity of papilledema.

Mild papilledema: Circumferential halo, elevation of nasal border, no major vessel obscuration.

Moderate papilledema: Circumferential halo, elevation of all borders, obscuration of one or more segments of major blood vessels leaving the disc.

Severe papilledema: Complete halo, elevation of whole nerve head, including the cup, total obscuration on the disc of a segment of a major blood vessel on the disc.[15]

The initial diagnosis also considered the risk factors of cerebral venous thrombosis (blood levels of protein C, protein S, homocysteine, antithrombin 3, factor 5 Leiden, anticardiolipin antibodies (ACLA), antinuclear antibody (ANA), lupus anticoagulant, pregnancy, malignancy, and drugs consumption). These were investigated and the results were recorded in a special questionnaire prepared for this purpose.

The patients were followed up during the first, third, sixth, and twelfth months of treatment for the presence of papilledema, using the ophthalmoscope.

The information was analyzed using the SPSS software version 22, T-test, and Chi-square tests.

Results

In this study, 65 CVT patients with a mean age of 37.6 ± 12.3 years were studied. Among them 30 patients (46.2%) suffered severe papilledema, with 21 mild papilledema (70%), two moderate papilledema (6.7%), a seven severe papilledema (23.3%). The mean ages of patients with and without papilledema were 35.6 ± 12.7 and 39.2 ± 11.9 years, respectively, and according to the *t*-test, no significant difference was observed between the two groups ($P = 0.25$). The sex ratio (female/male) in the two groups was 7/23 and 10/25, respectively, and according to the Chi square test, the difference between the two groups was not significant ($P = 0.63$). Figure 1 shows the frequency of symptoms in CVT patients. It is clear that the most common symptom is headache with a frequency of 92.3% and the least common symptoms are ataxia and quadriparesis with a frequency of 1.5%. Figure 1 shows the frequency of symptoms in patients with and without papilledema. The Fisher's exact test and Chi-square test on the data showed that no significant difference was observed between the two groups in terms of the frequency of symptoms in patients with papilledema and patients without papilledema ($P > 0.05$).

Of the 65 CVT cases studied in this research, 28 cases (43.1%) had a metabolic syndrome, 17 cases were non-papilledema, and 11 were papilledema patients (48.6 vs. 36.7%), but according to the Chi square test, no significant difference was observed between the two groups. Figure 2 shows the frequency of risk factors for CVT patients where the most common risk factors were high WC and OCP use. Table 1 shows the distribution of the mentioned risk factors for patients with papilledema and patients without papilledema. From the data, both the Fisher's exact and Chi-square test showed that none of the frequency differences of the risk factors in patients

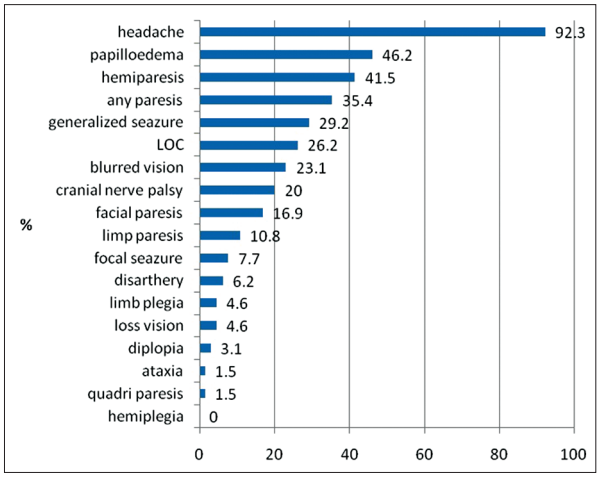

Figure 1: Frequency of symptoms in patients

with papilledema and patients without papilledema were statistically significant ($P > 0.05$).

As stated previously, the patients were followed up in the initial diagnosis of CVT, one, three, six, and twelve months later, in terms of progress or regress. The results of the regression of papilledema in the follow-up are shown in Figure 3. According to this figure, in patients with papilledema, the intensity is reduced as time passes.

Average duration of disease in patients with papilledema was 1.82 ± 3 months ranging from zero to twelve months. On the other hand, linear regression analysis of the data showed that none of the studied risk factors had a significant effect on the duration of papilledema. ($P > 0.05$)

Laboratory findings also indicated that one patient (1.5%) of the papilledema group had a positive ANA test. None of the patients had a positive anti-neutrophil cytoplasmic antibody (ANCA) test. On the other hand, four patients (6.2%) suffered from vasculitis, two of them were papilledema patients, but two were patients without papilledema (6.7 vs. 5.7%), and there was no significant difference between the two groups ($P = 0.99$).

In Figure 4, the frequency of the type of involved sinus is shown. On the basis of the above figure, the most common sinuses involved in the studied patients were sagittal and lateral sinuses (frequency = 30). In Table 2, the frequency distribution of the type of involved sinus based on papilledema and lack of papilledema is shown. Results show that the most common sinus involved in papilledema patients were sagittal and lateral sinuses that included 20 of the 30 patients, equivalent to 66.7%. However, the most common sinus involved in other patients without papilledema is a lateral sinus that included 14 of the 35

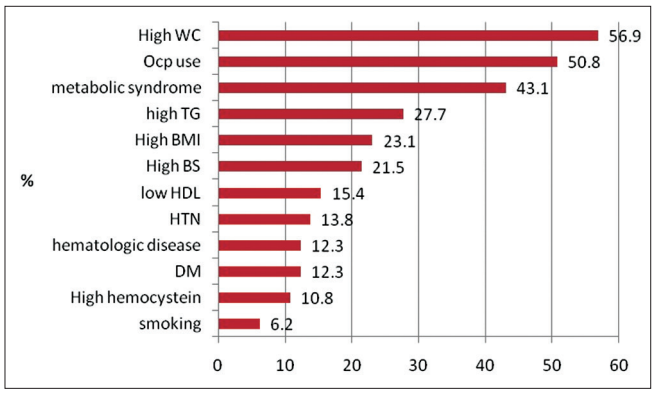

Figure 2: Frequency of risk factors of CVT in patients

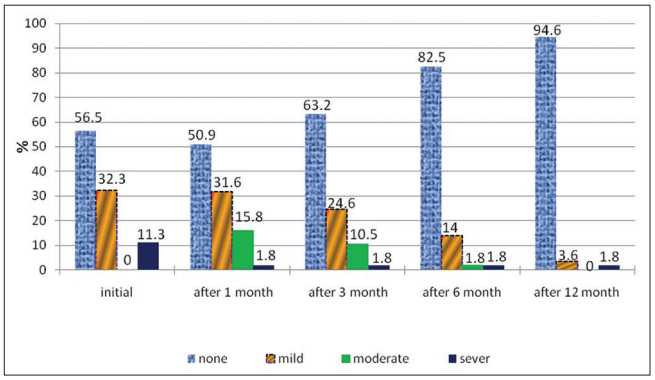

Figure 3: Frequency of papilledema severity up to one year after the incidence

Table 1: Distribution of clinical signs in patients with and without papilledema

Variables	Clinical signs			Risk factors			
Clinical signs papilledema	No *n* (%)	Yes *n* (%)	*P*	Factors	No *n* (%)	Yes *n* (%)	*P*
Focal seizure	1(2.9)	4(13.3)	0.17	Blood pressure	6(17.1)	3(10)	0.49
Generalized seizure	10(28.6)	9(30)	0.9	Metabolic syndrome	17(48.6)	11(36.7)	0.33
Headache	32(91.4)	28(93.3)	0.99	HDL Low	4(11.4)	6(24)	0.3
Cranial nerve palsy	7(20)	6(20)	0.99	TG High	11(31.4)	7(23.3)	0.47
Diplopia	2(5.7)	0(0)	0.5	BS High	7(20)	7(23.3)	0.75
Blurred vision	5(14.3)	10(33.3)	0.07	WC High	22(62.9)	15(50)	0.3
Vision loss	1(2.9)	2(6.7)	0.47	BMI High	9(25.7)	6(35.3)	0.07
Any paresis	15(42.9)	8(26.7)	0.17	Diabetes	5(14.3)	3(10)	0.72
Facial paresis	7(20)	4(13.3)	0.48	Smoking	3(8.6)	1(3.3)	0.62
Hemiparesis	18(51.4)	9(30)	0.14	OCP use	15(42.9)	18(60)	0.17
Hemiplegia	0(0)	0(0)	1	High homocysteine	6(17.1)	1(3.3)	0.11
Quadric paresis	1(2.99)	0(0)	0.99	History of abortion	4(11.4)	4(13.3)	0.99
Limb paresis	3(8.6)	4(13.3)	0.7	Lupus anticoagulant	2(5.7)	1(3.3)	0.99
Limb plegia	1(2.9)	2(6.7)	0.59	Antiphospholipid antibody	4(11.4)	3(10)	0.99
Ataxia	1(2.9)	0(0)	0.99	Anticardiolipin	9(25.7)	7(23.3)	0.82
Dysarthria	3(8.6)	1(3.3)	0.62	Anemia	7(20)	3(10)	0.54
LOC	12(34.3)	5(16.7)	0.11	Polycythemia	5(14.3)	0(0)	0.031

WC: Waist circumference, BMI: Body mass index, OCP: Oral contraceptive pil, LOC: Level of consciousness , HDL: High-density lipoprotein, TG: Thyroglobulin, BS: Blood sugar

Table 2: Distribution of the type of sinus involved based on the incidence and lack of papilledema

Sinus involved	No		Yes		Total	
papilledema	Numbers	Percentage	Numbers	Percentage	Numbers	Percentage
Sagittal	6	17.1	2	6.7	8	12.3
Lateral	14	40	5	16.7	19	29.2
Sagittal and lateral	10	28.6	23	76.7	33	50.8
DVT	3	8.6	0	0	3	4.6
All of the sinuses	2	5.7	0	0	2	3.1
Total	35	100	30	100	65	100

P=0.002. DVT: Deep vein thrombosis

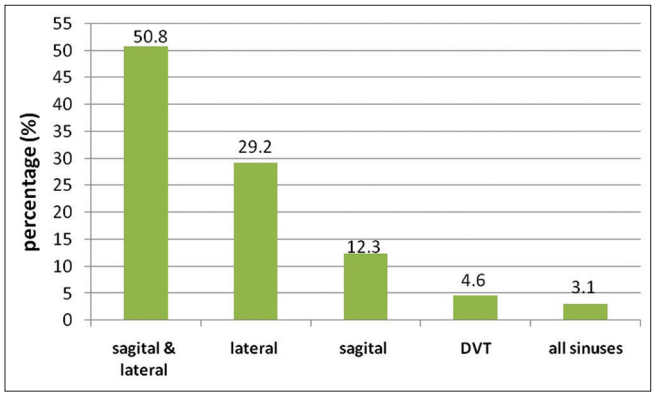

Figure 4: Frequency of the sinus involved in patients

or 40% of the patients. The Fisher's exact test on the data shows that the difference in the frequency of the involved sinus, based on the papilledema and lack of it in patients is significant (P = 0.002).

Discussion

The overall objective of this study was to determine the factors affecting the incidence of papilledema in patients with cerebral venous thrombosis. In this study from 65 patients under study, 30 patients (46.2%) suffered papilledema, with severe edema in seven patients (23.3%). Other studies have also shown that there is a relationship between the incidence of cerebral vein thrombosis and papilledema. In other words, papilledema is created as a result of increased intracranial pressure and with increased intracranial pressure the pressure is transported to the optic nerve sheath, damaging the axoplasmic transport of the optic nerve. Intra-axonal transport obstruction leads to the swelling of the axons and leak of water, proteins, and other cell contents in the extracellular space of the optic nerve and eventually causes edema in the optic nerve.[14] Christian *et al.*, in a study in 2011, estimated the incidence of papilledema in patients with CVT, as much as 20 to 30%.[4] In 2009, Ferro *et al.*, studied 624 patients with CVT, reporting the outbreak of papilledema in as much as 29%.[6] In the present study, there was no significant difference between the age and sex distribution of the two groups of patients with and without papilledema. The clinical signs observed in CVT patients, in both groups, also showed no significant difference. Notably, headache, papilledema, and hemiparesis were the most common clinical symptoms in these patients and the high incidence of papilledema could also be a clear indication of the relationship between cerebral venous thrombosis and papilledema. Buschi's study, in 2008, also marks papilledema as the third common symptom in patients with CVT. In this study, of the 12 identified risk factors, a high level of WC, oral contraceptive use, and metabolic syndrome, were the most common risk factors of developing CVT in patients. On the other hand, the most common sinuses involved in the patients were the sagittal and lateral sinuses. The most involved sinus in patients without papilledema was the lateral sinus, while the lateral and sagittal sinuses were mostly involved in patients with papilledema. In other studies, when the lateral sinus was involved, the frequent manifestations of the disease included background disease symptoms, such as, fever, natural symptoms, and discharge from the ear, while in case the superior sagittal sinus was involved, symptoms such as increased intracranial pressure and papilledema were considered among the most common symptoms.[10,11] However, the results showed that the frequency of CVT symptoms in both groups of patients (with papilledema and patients without papilledema) revealed no significant difference between them and from among the risk factors of CVT, only polycythemia was different in the two groups of patients with papilledema and patients without papilledema and the other factors were not significantly different.

Conclusion

The results of this study show that after one year of disease onset, two patients (3.6%) still had mild papilledema and one patient had severe papilledema, but due to the low number of cases with prolonged papilledema, it was impossible to examine the impact of the variables and risk factors of the disease. Therefore, this case was within the limitation of the present CVT study and studying a greater volume of patients with CVT is recommended for future studies.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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