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Original Contribution

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Systemic, secondary and infectious causes for cerebral vasculitis:

Clinical experience with 16 new European cases

Key words:

Systemic, secondary and infectious vasculitis, Behçet syndrome, giant cell arteritis, Wegener's granulomatosis, Churg-Strauss-syndrome, systemic lupus erythematoses, sarcoidosis, ANA-positive systemic vasculitis, borreliosis, syphilis.

Background and Purpose: Cerebral vasculitis represents a rare form of vascular inflammatory involvement caused by heterogeneous conditions. In this study the wide spectrum of cerebral vasculitis despite primary angiitis of the CNS is analysed.

Methods: Our cohort included 16 white patients with cerebral vasculitis treated in a single German institution between 2003 and 2008. Clinical and diagnostic features were obtained by retrospective chart review; follow-up information and outcome were obtained prospectively.

Results: The spectrum of conditions responsible for cerebral vasculitis included 7 patients with Behçet syndrome and single cases of giant cell arteritis, Wegener's granulomatosis and Churg-Strauss-syndrome, respectively. Vasculitis secondary to systemic diseases included two patients with systemic lupus erythematoses, one patient with sarcoidosis and one patient with ANA-positive systemic vasculitis. Two patients suffered from infectious angiitis caused by borreliosis and syphilis. The mean age at onset of cerebral symptoms was 41.38 years. The most frequent clinical symptoms were headache, gait disturbances and unilateral numbness. None of the patients with Behçet-syndrome experienced any ischemic event which was a significant difference compared with the other patients ($p=0.011$). Gadolinium enhancing lesions were significantly more frequent in Behçet-syndrome compared to the other types of vasculitis ($p=0.041$). There was no significant difference between vasculitis patients with or without Behçet-syndrome regarding outcome parameters.

Conclusion: The differential diagnosis of conditions responsible for cerebral vasculitis includes a wide spectrum of diseases. Clinical features and course of cerebral vasculitis are highly variable. The enigma of cerebral vasculitis will only be solved by implementing large prospective multicenter databases.

Most strokes are attributed to arteriosclerosis or brain embolism. As an uncommon cause of stroke or cerebral inflammation cerebral vasculitis may be considered. Primary central nervous system vasculitis also known as primary or isolated angiitis of the central nervous system (PCNSV) is often considered in the diagnosis of cerebral vasculitis[3]. But what conditions despite PCNSV are responsible for cerebral vasculitis? These afflictions remain poorly recognized. Heterogeneity of the disease is responsible for a lack of uniform diagnostic criteria and treatment recommendations. Our existing knowledge is based on incompatible and small case series or single case reports[3]. Cerebral vasculitis is still a major diagnostic and therapeutic challenge and is magnified by numerous unanswered questions regarding epidemiology, predisposition, pathophysiology and outcome. As we frequently are asked to re-evaluate patients with uncommon causes of stroke we had the opportunity to evaluate 16 patients with cerebral vasculitis despite PCNSV treated within the short period of 5 years.

Material and Methods

Patient Selection

Sixteen consecutive patients diagnosed as cerebral vasculitis from 2003 through 2008 in the Alfried-Krupp-Hospital, Essen, Germany, were recruited in this study. We excluded 21 patients in which PCNSV was diagnosed and patients in which the diagnosis of CNS vasculitis were not definite. Patients with systemic vasculitis without CNS involvement were also excluded from this analysis.

Clinical Data Collection

In living patients diagnosed > 1 year before data collection we tried to obtain follow up information by telephone interview or from outside hospital charts. In living patients diagnosed < 1 year before data collection, the requested features were obtained from recent clinical visits. Evaluation was focused on demographic, clinical and outcome features. Analysis included demographic data like sex and age at first cerebral symptom presentation, clinical presentation at onset of disease and during follow-up period, results from MRI, angiography, CNS biopsy and laboratory investigations. Furthermore treatment data were collected. Functional status at first visit and latest follow-up was classified by using the modified Rankin score (MRS).

Statistics and Data Analysis

Statistical analysis was completed with SPSS version 17.0. Statistical comparisons of categorical information were done using Chi-Quadrate-test or Fisher's exact test when samples were small. Comparisons were made using the Mann-Whitney U test (Wilcoxon test) for numeric data. $P < 0.05$ was considered to be statistical significant, $p < 0.06$ was regarded as trend to significance. All p values were two-sided.

Results

Demographic data and diagnosis

The heterogeneous group of patents included 10 patients with a primary vasculitis. There were 7 cases of Behçet-syndrome and single cases of giant cell arteritis, Wegener's granulomatosis or Churg-Strauss-syndrome, respectively. Vasculitides secondary to systemic disease were diagnosed in two patients with systemic lupus erythematosus, in one patient with sarcoidosis and one patient with ANA-positive

systemic vasculitis. Two patients presented with infectious angiitis in borreliosis and syphilis.

The mean age of the 16 patients at time of cerebral symptom onset was 41.38 years (median 39 years, range 27-70 years). The mean age at cerebral symptom onset of the 7 patients with Behçet-syndrome was 37.43 years (median 33 years, range 27-55 years), the mean age of the non-Behçet-patients was 44.44 years at cerebral symptom onset (median 42.0 years, range 35-70 years). The gender distribution of all patients was 1:1, in Behçet-syndrome males were more frequent with 71.4%, and in non-Behçet-patients females were more frequent with 66.7%. One patient was of Spanish, 4 of Turkish or Kurdish (25.0%) and 11 patients (68.8%) of German family origin. All patients with Turkish or Kurdish family origin had Behçet-syndrome, so 57.1% of all patients with Behçet-syndrome had Turkish or Kurdish ancestors. The mean follow up period was 54.5 months (median 22.5 months, range 1-240 months). There was a statistical significantly difference with a longer follow-up in patients with Behçet-syndrome (mean 102.71 months, median 120 months, range 1-240 months) compared with non-Behçet-patients (mean 17 months, median 7 months, range 2-75 months) ($p=0.031$). Cerebrovascular risk factors were present in 6 of 16 patients (37.5 %) which were smoking in 5 patients (31.3%) and arterial hypertension in 3 patients (18.8%). There was no statistical difference regarding age, sex and frequency of cerebrovascular risk factors in patients with or without Behçet-syndrome. Cerebrovascular risk factors were not related to the frequency of strokes, transient ischemic attacks, microangiopathy or diffusion disturbances in MRI, or death.

Clinical Symptoms

The clinical presentation of CNS vasculitis was highly variable. The most frequent clinical symptoms over the whole follow up period were headache (56.3%), gait disturbances (62.5%) and unilateral numbness of the body (50%). Clinical symptoms at onset of disease were similar to clinical features during follow-up. Ischemic events like stroke or transient ischemic attack were infrequent (37.5%). None of the patients with Behçet-syndrome experienced an ischemic event which was a significant difference compared with the other patients ($p=0.011$). One patient with Behçet-syndrome presented with recurring aseptic meningitis. Almost all patients with Behçet-syndrome suffered from headaches which represented a significant difference compared to the other vasculitis patients ($p=0.011$) during the follow-up period and a trend to significance ($p=0.06$) in the whole observation period. None of the patients characterised headache as “thunderclap” headache.

Only one patient (the one with Wegener’s granulomatosis) experienced an intracerebral hemorrhage.

There was no other statistical difference in cerebral symptoms observable between patients with Behçet-syndrome and the other vasculitis patients.

However as the group of patients had cerebral vasculitis due to different underlying conditions, they widely differed by the additional systemic symptoms.

The patient with Wegener’s granulomatosis showed cerebral vasculitis with repeated intraparenchymal hemorrhages in a late stage of the disease (25 years after first systemic symptoms). No other reasons (medication-side-effect or coagulation disturbances) for neurological symptoms despite vasculitis were found. She also showed mixed axonal and demyelinating polyneuropathy, symptomatic seizures and reactive depression. Furthermore she suffered from chronic sinusitis and from serious lung and kidney involvement with pulmonal bleedings, secondary glomerulonephritis with dialysis and kidney transplantation. In the two female patients

with systemic lupus erythematosus (SLE) one presented with cognitive decline, hemiparesis, symptomatic seizures and interstitial myositis due to biopsy-proven vasculitis more than 20 years after retrospective described onset of systemic symptoms but was firstly diagnosed at that time. Her history was significant for livedo racemosa, chronic polyarthritis and two spontaneous abortions (without evidence of antiphospholipid antibody syndrome). The other patient with systemic lupus erythematosus had a history of pericarditis and polyarthritis and presented with cerebral vasculitis 14 years after establishment of diagnosis. In the patient with cerebral vasculitis due to sarcoidosis stage IV symptoms included kidney insufficiency with IgA nephritis and interstitial nephritis, atrioventricular block and anaemia. The patient with cerebral vasculitis due to Churg-Strauss-syndrome with repeated transient ischemic attacks also showed polyneuropathy with histological detection of small vessel vasculitis. Further clinical hallmarks in this patient were allergic diathesis, asthma and sinusitis. In this patient diagnosis of Churg-Strauss-syndrome was not established until neurological symptoms appeared. In the 7 patient with Behçet-syndrome all presented with recurrent aphtous stomatitis, 4 patients (57.1%) with genital ulcerations, 3 patients (42.8%) with eye lesions (uveitis, retinal vasculitis, optic nerve neuritis, retinal periphlebitis) and 3 patients (42.8%) with skin lesions (folliculitis, erythema nodosum). Only two patients showed positive pathergy testing but the other tests were partly performed after the initiation of immunosuppressive treatment. Despite mucocutaneous signs only the three patients with eye involvement consulted a healthcare consultant earlier. In the others, Behçet-syndrome was not diagnosed until neurological involvement occurred. In the patient with ANA-positive cerebral vasculitis and in the two patients with infectious vasculitis due to syphilis and borreliosis no other systemic symptoms were detectable. Our

male patient with giant cell angiitis suffered from bitemporal headaches and fever for two weeks before stroke.

Magnetic resonance findings

MRI was performed and revealed abnormal findings in all patients (100%). Ischemic infarctions were the most frequent observed signs in MRI in the group of patients with vasculitis without Behçet-syndrome (77.8%) while no patient with Behçet-syndrome presented with infarctions in MRI ($p=0.003$). In contrast to this gadolinium enhancing lesions were significantly more frequent in Behçet-syndrome (85.7%) compared with the other types of vasculitis (22.2%) ($p=0.041$). Signs of microangiopathy were also frequently observed in MRI (56.3% for all, 42.9% in Behçet-syndrome, 66.7% in non-Behçet-vasculitides, respectively). Almost all patients showed bilateral MRI abnormalities (81.3%).

Conventional cerebral angiography

Conventional cerebral angiography was carried out in 6 of 15 documented patients (40%). Almost all of them were performed in non-Behçet-syndrome-patients. 5 of 8 patients with cerebral vasculitis due to other causes despite Behçet-syndrome underwent angiography (62.5%) which was indicative for vasculitis in all of them. In one patient diagnosed as having Behçet-syndrome an old carotid artery dissection was evident in angiography. Some days after angiogram ICA dissection of the other side appeared without documented complications in the course of angiography or any adequate trauma.

Histological Features

CNS biopsy was performed in only 2 of 15 documented patients (13.3%). Histopathological examinations revealed the definite diagnosis of cerebral vasculitis

in both cases. A peripheral biopsy was histological analysed in 5 of 15 documented cases (33.3%) and documented vasculitis in all 4 vasculitis-patients with non-Behçet-syndrome.

Laboratory and Cerebrospinal Fluid Studies

In 13 of 16 patients (81.3%), CSF examinations were performed and disclosed abnormal findings (cell count > 5 cells / μ l or total protein concentration > 45 mg/dl) in 12 of them (92.3%). Samples were obtained in all 7 patients with Behçet-syndrome and were indicative for inflammation in all of them. In the other patients, 5 of 6 examinations (83.3%) revealed pathological results. The typical finding in CSF was a mild lymphocytic pleocytosis combined with an elevated protein level. The mean cell count was 51.27/ μ l (median, 28/ μ l, range, 7-148/ μ l), the mean concentration of total protein was 133.4 mg/dl (median, 73.0 mg/dl, range 56-317 mg/dl). There was no significant difference between patients with and without Behçet-syndrome regarding cell count and protein level. Oligoclonal banding was found in 33.3% of patients (33.3% in Behçet-syndrome, 33.3% in non-Behçet-syndrome). Laboratory screening was unremarkable for complement factors C3 and C4, antinuclear antibodies, antibodies to extractable nuclear antigens, antineutrophil cytoplasmic antibodies and HIV in all patients with Behçet-syndrome. Antinuclear antibodies, rheumatic factors, antibodies to extractable nuclear antigens and antineutrophil cytoplasmic antibodies were partly elevated in the other vasculitis patients.

Treatments

Thrombocyte antiaggregation drugs were prescribed in 4 of 16 patients (25%). An immunosuppressive therapy was documented in the grand majority of patients (81.3%). In detail, these included intravenous glucocorticoid therapy in 62.2%, oral

glucocorticoid therapy in 56.4%, intravenous and/or oral cyclophosphamide in 18.8%, azathioprin in 37.5% of the patients. The two patients with cerebral vasculitis due to infectious diseases (neurosyphilis and borreliosis) were treated with antibiotic drugs. A positive response to therapy was noted in 15 of 16 patients (93.3%). There was a statistical significant difference observable in patients with Behçet-syndrome compared with the other vasculitis patients regarding the higher incidence of azathioprin treatment in Behçet-syndrome (71.4% versus 11.1%, $p= 0.043$). No biologicals were given in this series of patients.

Outcome

Complications of treatment or diagnostic procedures were recognized over the course of the disease in 4 of 16 cases (20%). As mentioned before one patient diagnosed as Behçet-syndrome experienced ICA dissection after angiography without adequate trauma. The patient with sarcoidosis acquired a lung aspergillosis associated with immunosuppression. After paused immunosuppression due to treatment of aspergillosis sarcoidosis worsened with newly affection of cerebral vessels. Two patients died within the documented follow-up. Both of them had systemic diseases with cerebral manifestation (Wegener's granulomatosis and sarcoidosis) with serious organ involvement (kidney and lung) and died due to non-cerebral disease progression. Modified Rankin disability scores were assessed at first presentation and at the last follow-up examination. Median MRS was 1 (mean, 1.47; range, 0-4) at first presentation and 1 (mean, 1.67; range, 0-6) at last visit information. There was no significant difference between those vasculitis patients with or without Behçet-syndrome.

Discussion

Cerebral vasculitis is a heterogeneous disease in which inflammation is caused by a wide range of causes. This analysis was focussed on patients in which cerebral vasculitis was not diagnosed as “isolated angiitis of the CNS” also called “primary angiitis of the CNS”. The spectrum of differential diagnose includes the primary systemic vasculitides, vasculitis in collagen vascular diseases, infectious vasculitis, vasculitis associated with neoplasia and vasculitis associated with drug abuse or treatment. The clinical presentation of cerebral vasculitis is highly variable; the differential diagnostic considerations are numerous.

It is interesting that Behçet-syndrome is the most frequent cause for cerebral vasculitis in our cohort. Despite the possibility of referring bias in the Rhine-Ruhr-area with a great part of the population with Turkish or Kurdish ancestors, it is important to consider in the differential diagnosis even in patients without Mediterranean family origin. In our cohort 4 of 7 Behçet-patients (57.1%) ethnic background was Turkish or Kurdish while the remaining 42.8% were Germans. Behçet-syndrome is a multisystemic vasculitis of the small-sized vessels. Venous involvement is typical in Behçet-syndrome; arterial participation is extremely rare. Neurological involvement may occur within the nervous parenchyma (neuro-Behçet) or in the cerebral vascular system (vasculo-Behçet) with a great incidence of cerebral sinus and venous thrombosis[14]. In our cohort all but one patient suffered from parenchymal neuro-Behçet; one patient showed recurrent aseptic meningitis. One patient presented with the very rare arterial involvement with arterial dissections[2]. Neuro-Behçet begins months or years after the mucocutaneous manifestations. As seen in our patients often neurological involvement can also be the first occasion for consulting healthcare consultants. Another diagnostic challenge may be the mild or incomplete mucocutaneous presentation. The meningoencephalitis predominates in the brainstem and is characterized by a variety of symptoms including headache[7]. In our

cohort no patient with Behçet-syndrome presented with MR-tomographic signs of infarction but showed significant more gadolinium enhancing lesions. As the diagnosis of neuro-Behçet is entirely based on clinical grounds this disease is the only one type of the cerebral vasculitis in which cerebral angiography and CNS biopsy are not required to perform. Cerebral arterial manifestations such as aneurysms and arterial dissections are extremely rare in this venous vasculitis. In the affected arteries, active arteriitis occurs initially, followed by destruction of the media and fibrosis[2, 7]. Cerebrospinal fluid studies showed pleocytosis and infrequent oligoclonal bandings. The absence of more than two oligoclonal immunoglobuline G bands was referred as indicative for neuro-Behçet in differential diagnosis to multiple sclerosis. But the amount of 33.3% of patients with positive oligoclonal bands in our cohort once more demonstrates the difficulties in diagnosis. Whether the substances used for the mucocutaneous manifestations also are effective in treating CNS manifestations has not been studied in larger trials. In neuro-Behçet, combinations of high doses of corticoids and immunosuppressive drugs are recommended. Ciclosporin A should not be used in the treatment of neuro-Behçet patients because of its potential neurotoxicity[6]. In our cohort patients with Behçet-syndrome were often treated with azathioprin. There was no significant difference between patients with Behçet-syndrome and those with other vasculitis regarding outcome features. Our cohort included also one patient with histology-approved cerebral giant cell arteritis. Brain infarction is a well-recognized complication of temporal arteritis but may also be the initial presentation of temporal arteritis. Color duplex sonography showed stenosis of MCA-M1-segment on both sides. His cerebral angiography revealed the typical picture of cerebral vasculitis in the peripheral arteries predominantly in the MCA of both sides. Laboratory investigations showed mild elevated C-reactive protein and almost normal ESR. Cerebrospinal fluid studies

showed pleocytosis (115 cells/ μ l) and mild elevated total protein (72.4 mg/dl). Brain biopsy approved giant cell arteritis. Color duplex sonography of temporal artery performed after receiving this result demonstrated typical dark halo indicative for temporal vasculitis. This case is very elucidating because it shows how important it is to think of giant cell arteritis even in uncommon cases. In this patient, an earlier performed temporal duplex sonography would have prevented him from invasive procedures like cerebral angiography and brain biopsy. However, this case is exceptional because the young age of the patient, the almost normal ESR and the intracranial vessel involvement. All these facts are extremely rare but have been reported[8, 10, 16]. Approximately 4% of patients with temporal arteritis experience transient ischemic attacks or strokes. The posterior circulation is the classical territory for strokes due to temporal arteritis, extracranial vertebral arteries are commonly affected[12].

Another extremely rare cause for cerebral vasculitis is Churg-Strauss syndrome (CSS). CSS typically presents with allergic diathesis, asthma and polyneuropathies of the multiplex type[9]. Our male patient presented with biopsy-approved peripheral involvement but showed also cerebral vasculitis with transient ischemic attacks. In a case series by Sehgal et al (1995), brain infarcts were seen in 3 of 47 patients[13]. There are few other case reports about CNS involvement of CSS[9, 17].

Another patient presented with cerebral hemorrhage due to vasculitis in very severe case of Wegener's granulomatosis. As in this patient neurological symptoms typically occur in the stage of generalization. This patient died due to systemic progression of the disease. The other patient who died due to systemic disease progression and treating complications was the patient with severe systemic sarcoidosis. CNS involvement occurs in approximately 5% of patients with sarcoidosis[11, 15]. The most common neurological manifestations of sarcoidosis are cranial neuropathies

(50-75%) and parenchymal involvement (overall 50%)[11]. Stroke is, however, an exceedingly rare complication of neurosarcoidosis, with very few case reports in the literature. Mechanisms responsible for stroke in sarcoidosis may be in situ thrombosis from perivascular granulomatous inflammation, cardiogenic emboli, large-artery compression or artery-to-artery emboli[11, 15]. Occurrence of angiitis as demonstrated in our patient has been reported extremely rare[4].

Our cohort included two patients with cerebral vasculitis due to SLE and one patient with ANA-positive vasculitis not fulfilling SLE criteria. SLE is generally considered in the evaluation of stroke in young patients[1]. SLE is a actually relatively uncommon etiology of stroke, even in young persons, being found in only 3.5% of stroke patients before the age of 45[1]. True vasculitis is an overestimated association in patients with stroke in SLE. Careful evaluation for cardiogenic emboli, hypercoagulable states, and arteriosclerosis should be performed. In SLE, strokes are often caused by a secondary antiphospholipid syndrome. According to our experience most patients referred to us do not have true cerebral vasculitis in SLE.

Our cohort also included two patients with cerebral vasculitis due to infectious diseases. The incidence of strokes in meningovascular syphilis is reported to range from 7% to 23%[5]. The cause of most cerebrovascular disease is syphilitic endarteriitis. The middle cerebral artery is the most commonly involved vessel leading to stroke[5]. In our patient occlusion of left PCA was documented in angiography. The other patient with vasculitis due to infectious disease had neuroborreliosis. Since the first description of meningovascular neuroborreliosis in 1987 reports of at least another 32 patients with meningovascular neuroborreliosis have appeared[5]. As in SLE, in clinical practise neuroborreliosis is widely overestimated since it is extremely rare in differential diagnosis of uncommon strokes and true vasculitis.

In conclusion, the spectrum of differential diagnosis includes wide range of diseases. As cerebral vasculitis is a heterogeneous group of disorders the clinical presentations can be highly variable and different diagnostic approaches are necessary. Cerebral angiography and brain biopsy are the diagnostic gold standard in cerebral vasculitis but in Behçet-syndrome these are not required. In some types of systemic vasculitis a muscle and nerve biopsy can reveal the diagnosis and so brain biopsy is not obligatory. However, in these cases it is important to consider if cerebral involvement is really caused by the systemic disease and to exclude other possible origins like medication-side effects, coagulation disturbances or arteriosclerosis.

Our investigation has a number of limitations. Most of the data were assessed retrospectively, prospective follow-up was incomplete. The possibility of referral bias has to be calculated. Our investigation is elucidating and valuable because it represents one of the most detailed descriptions of European patients with cerebral vasculitis from a single center.

The strength of our study is the large number of consecutive patients treated over the short period of 5 years. A further strong point in our analysis is the attempt to measure prospective data. Furthermore this study clearly points out the remaining deficits in knowledge of the disease. To date it is still a challenge to diagnose, treat and follow-up patients thought to have cerebral vasculitis. Due to the missing clinical guidelines and the rarity of these diseases diagnosis and treatment should be reserved to centers with great expertise in vasculitis. Furthermore the complex nature of the disease requires an intensive multiprofessional approach with good cooperation of neurological, rheumatologic, neurosurgical and neuroradiological experts in this field. In order to solve some aspects of its enigma, a prospective multicenter collaborative study collecting patients suspected to have cerebral vasculitis as recent demanded by Berlit[3] is urgently needed.

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