eNeurologicalSci 13 (2018) 26–30

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci

Ischemic stroke as initial manifestation of systemic lupus erythematosus: A case report and review of the literature

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ARTICLE INFO

Keywords:
Ischemic stroke
Systemic lupus erythematosus
Initial manifestation
Stroke in young patient

ABSTRACT

Stroke is a frequent occurrence among patients suffering from systemic lupus erythematosus (SLE), but it rarely occurs as the initial manifestation of the disease. We here present the case of a 37 year-old patient who developed an acute cerebellar ischemic stroke as initial event of SLE: elevated partial thromboplastin time and ESR, thrombocytopenia, anti-ds-DNA, anti-SSA, anti-JO-1, and the lupus anticoagulant were detected, and the diagnosis of SLE was established. In addition, we reviewed the literature in order to clarify the demographic, clinical, imaging and outcome characteristics of such a presentation, and found 10 similar cases. Most patients were young (age 31.7 ± 8.5 years) and women (8/11, 72.7%). Stroke most often affected the vertebrobasilar territory (7/11, 63.6%). The stroke mechanism was not clearly defined in these cases. Treatment with immunosuppression and anticoagulation was considered to be a reasonable choice for early secondary stroke prevention. The occurrence of ischemic stroke, primarily in the vertebrobasilar system among young patients, especially women, should always raise suspicion for underlying SLE, and prompt diagnostic investigations to confirm or exclude its presence.

1. Introduction

Systemic Lupus Erythematosus (SLE) is characterized by systemic inflammation, auto-antibodies and a relapsing-remitting course. SLE most often affects young women and is characterized by multi-system involvement. The central nervous system (CNS) is a frequent target of SLE, and its involvement leads to increased rates of morbidity and mortality [1].

Stroke events are frequent among patients suffering from SLE, affecting 3–20% of them, mainly in a young for stroke population, and usually within the first 5 years from diagnosis [1–4]. The diagnosis of SLE is usually established before any stroke occurrence [5]. The risk of stroke is 8 times higher in SLE patients compared to the general population [3], and the risk for cardiovascular events is increased by 3% every year after diagnosis [1]. All these are responsible for 20–30% of deaths among SLE patients [1].

There are several potential mechanisms for cerebrovascular disorders in SLE, including hypercoagulable states, cardiogenic embolism, premature or accelerated atherosclerosis, and rarely vasculitis [3]. The clinical expression is also variable as SLE can cause transient cerebral ischemia (TIA), arterial ischemic stroke, intraparenchymal hemorrhage, subarachnoid hemorrhage, and cerebral venous thrombosis [1].

While cerebrovascular vascular events are common among patients with SLE, ischemic stroke as the first manifestation of the disease is rare and it can often be misdiagnosed. We here present the case of a young patient who developed an acute cerebellar ischemic stroke as initial manifestation of SLE, and review the literature in order to identify the demographic, clinical, imaging and outcome characteristics of such a presentation.

2. Methods

We present the case of a young patient who developed an acute cerebellar ischemic stroke and was subsequently diagnosed with systemic lupus erythematosus. In addition, we performed a literature search in the database PubMed using the terms “stroke AND lupus AND first manifestation”, “stroke AND lupus AND initial manifestation”, “vascular AND lupus AND initial manifestation”, and “vascular AND lupus AND first manifestation”. We reviewed all papers published in the English language and also their references in order to discover additional cases.

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https://doi.org/10.1016/j.ensci.2018.11.001
Received 18 October 2018; Accepted 1 November 2018
Available online 09 November 2018

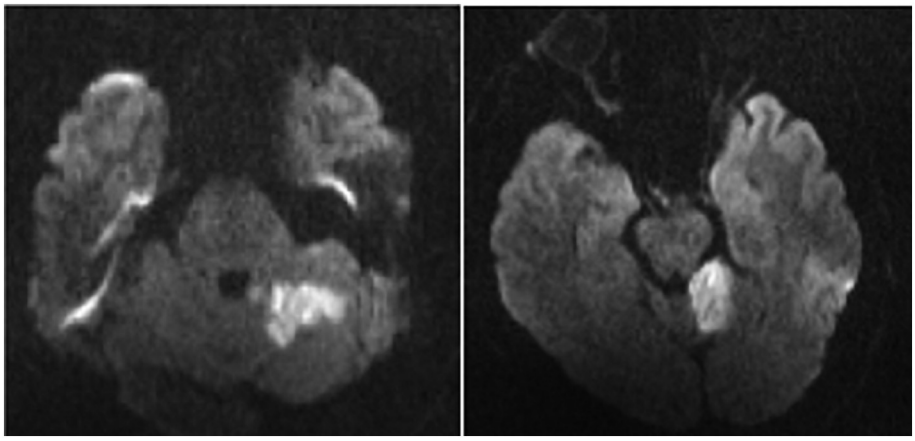

Fig. 1. MRI DWI showing an acute ischemic lesion in the territory of the left superior cerebellar artery.

3. Results

3.1. Case report

A 37-year-old man presented to the emergency department complaining of acute onset dizziness, gait instability and vomiting. He was previously diagnosed with rheumatoid arthritis and hypothyroidism and received methotrexate occasionally. His father had dyslipidemia and coronary artery disease and his mother was diagnosed with SLE. General physical exam was unrevealing. Neurological examination revealed left hemiataxia and gait ataxia, with otherwise unremarkable findings. Admission NIHSS score was 2.

Brain MRI demonstrated acute ischemic infarct in the territory of the left superior cerebellar artery (SCA) (Fig. 1).CT angiography revealed no large vessel occlusion, aneurysm or dissection. Admission laboratory tests revealed elevated partial thromboplastin time (56.2 s), mild elevation of ESR (26 mm/1st hour), thrombocytopenia (100.000/μL, down from 415,000/μL 7 days earlier), strongly positive anti-ds-DNA (409WHO/mL), anti-SSA (102.5 U/mL), anti-JO-1 (94.6 U/mL), and presence of lupus anticoagulant. Testing for protein-C, protein-S, anticardiolipin antibodies and anti-β2-GPI, CRP, rheumatoid factor, anti-Sm, anti-RNP, anti-SSB, anti-Scl, ANCA, AMA, ASMA, and direct Coombs revealed negative results. Transthoracic and transesophageal echocardiography were unremarkable.

During hospitalization, pancytopenia was observed. The diagnosis of SLE was established, according to the Systemic Lupus International Collaborating Clinics Classification (SLICC) criteria [6]. He was treated with high-dose intravenous corticosteroids, followed by oral prednisolone, and hydroxychloroquine, as well as IV heparin and subsequently acenocoumarol. The patient experienced gradual clinical and laboratory improvement. Follow up at three and twelve months revealed no neurological or functional abnormalities. The NIHSS score was 0.

3.2. Review of the literature

We identified 10 reported cases of stroke as initial event of SLE. These are summarized in Table 1, where we also include our patient.

The mean age was 31.7 ± 8,5 years. Eight of 11 (72,7%) patients were women. In seven (63,6%) patients the affected arterial territory was the vertebrobasilar.

CT or MRI scans results were reported in 9 patients and their findings were: multiple vertebrobasilar infarcts in more than one arterial territory (n = 6), single cerebral lobar infarct (n = 2), and no abnormal findings (n = 1). The most frequently affected area was the pons.

Angiographic studies were reported in 8 patients and their findings were: stenosis of a single vessel of the vertebrobasilar system (n = 3), multiple stenosis involving both vertebrobasilar and carotid system (n = 1), bilateral occlusion of vertebral arteries (n = 1), left internal carotid artery occlusion (n = 1), and no abnormal findings (n = 2). The vertebral arteries were the most commonly affected arterial structure (4 of 8 studies).

Reported laboratory findings were: positive anti-ds-DNA (n = 7), C3 and C4 protein depression (n = 6), elevated ESR (n = 5), positive antinuclear factor (n = 4), elevated DNA binding (n = 3), thrombocytopenia (n = 2), and lupus anticoagulant (n = 2).

Treatment choices were reported in only 4 cases. In all, immunosuppressant therapy was used [IV prednisolone followed by oral prednisolone (n = 1), oral prednisolone (n = 2) and IV cyclophosphamide (n = 1)]. This was combined with IV anticoagulation followed by oral anticoagulation (n = 1), oral anticoagulation (n = 2) and dipyridamole (n = 1).

Follow up data were scarcely documented. TIAs were reported in two cases (one with 2 episodes within 16–19 months, one with 5–6 episodes within 12 months). More permanent deficits were reported in two cases (in one case ataxia and dysarthria were reported at 6 months and in the other the patient was able to stand and walk with assistance at 9 months). Long-term cognitive impairment was reported in two cases. In our patient, no abnormal signs were found at the 3-month and 12-month follow-up, indicating fully recovery.

4. Discussion

Ischemic stroke as initial manifestation of SLE is an uncommon occurrence. It usually affects patients who are young, mostly women, and predominantly involves the vertebrobasilar territory. Treatment with immunosuppression and anticoagulation is a reasonable initial therapeutic approach.

It is not unusual to encounter ischemic stroke in the course of SLE [3,5,7]. This may be in part related to SLE disease activity and in part to the operation of classic stroke risk factors, such as hypertension, dyslipidemia and others, which often accompany SLE and its treatment [8,9]. However, it is very rare to encounter stroke as the initial event of the disease. The paucity of reported cases attests to this fact.

Stroke most often affects patients who are young, especially women. These demographic characteristics parallel those of the SLE population and are indirectly convincing that the stroke event was directly linked with SLE [10].Also, our patient was young, had predisposition to autoimmune diseases and no other obvious factors for vascular events were found. These facts convinced us that the underlying etiology was the presence of active SLE.

It has been described that in SLE ischemic stroke is caused by several diverse mechanisms, including cardioembolism, large artery stenosis of either non-atherosclerotic or atherosclerotic etiology, arterial

Table 1
Summary of all reported patients with ischemic cerebrovascular event as initial manifestation of SLE.

Demographics relevant past history	Initial ischemic cerebrovascular event	Neuroimaging findings	Laboratory investigations	Treatment, follow-up & neurological outcome
29 y/o man [5]	• Transient quadriparesis, unable to move jaw or speak • Transient vertebrobasilar ischemia after 5 months	• Cerebral &left carotid angiography: normal	• Positive antinuclear factor • Elevated DNA binding • Leukopenia, lymphopenia • C3 protein depression • Findings in renal biopsy • Normal ESR	• Treatment not reported • Two TIAs after 16–19 months • Focal seizures after last episode
32 y/o woman, pregnant [5]	• Transient left hemiparesis in immediate postpartum period	• CT scan: normal	• During pregnancy: Positive WR and VDRL, mild thrombocytopenia (30 × 10^9/l), positive antinuclear factor • Normal ESR • Three months postpartum: Severe thrombocytopenia (10 × 10^9/l), elevated DNA binding, positive anti-Sm antibody, C3 and C4 protein depression	• Three months postpartum: Prednisone 60 mg per day, reducing to 10 mg per day. • Five or six TIAs within the next 12 months • Dipyridamole 400 mg per day was added. • No further events for the next 8 months
41 y/o woman, history of hepatitis and seronegative polyarhtritis [5]	• Recurrent episodes of right hemiparesis [3] during 3 years	• CT scan: cerebral atrophy, right temporo-parietal infarct	• Normal ESR • Anti-Sm antibody absent • IgG elevation • Findings in renal biopsy • DNA binding elevation • Positive anti-ds-DNA • Positive LE cells	• Treatment not reported • Persistent right facial weakness • Progressive dementia followed
46 y/o woman, history of paranoid psychosis [5]	• Bilateral retinal artery occlusion • Epileptic seizures occurred 15 days after • Transient right hemiparesis 1 day later	• Serial isotope scans: right frontal lobe infarct • CT scan at the age of 52 y/o: severe cerebral atrophy, infarcts in both temporal, left frontal and left parietal lobes.	• Elevated ESR • Three months later: positive antinuclear factor, elevated DNA binding, positive WR, C3 and C4 protein depression, renal function impairment • Findings in renal biopsy	• Treatment not reported • Focal and generalized seizures after 3 years, associated with prednisone-induced hyperglycemia and severe hypertension. • Aphasia, cognitive impairment, apraxic gait, bilateral extensor plantar response
16 y/o woman, history of skin red rash after sunlight exposure [4]	• Multiple episodes of dizziness and headache • Acute dysarthria and quadriataxia.	• MRI: multiple vertebrobasilar territory infarcts • Cerebral angiography: stenoses of left MCA, left vertebral, basilar and right PCA • MRI scan at the age of 19 y/o: no additional lesions	• Leukocytosis • Positive ANA • Positive anti-ds-DNA • Positive direct Coombs Test • Positive lupus anticoagulant	• Oral anticoagulation • IV cyclophosphamide monthly • 6-months follow-up: ability to walk, ataxia, dysarthria • No further events for the next 3 years
26 y/o woman [4]	• Acute headache, dizziness, dysarthria, quadriataxia.	• MRI: multiple vertebrobasilar territory infarcts • Cerebral angiography: occlusion of bilateral vertebral arteries	• Anemia • Leukocytosis • Elevated ESR • Weakly positive anti-ds-DNA • Positive ANA • Positive direct Coombs Test • Lupus anticoagulant absent	• Antihypertensives, warfarin plus prednisolone • 9-months follow-up: ability to stand and walk with assistance
24 y/o woman [12]	• Acute headache, right hemiparesis and gait ataxia.	• CT scan: normal • MRI: bilateral pontine infarcts • CTA: basilar artery stenosis	• Weakly positive ANA • Positive anti-ds-DNA • C3 and C4 protein depression • Normal ESR	• Heparin IV, initially • Further treatment not reported • Follow-up not reported
34 y/o man [12]	• Acute headache, dizziness, right hemi-and gait ataxia, dysphagia and righthypesthesia	• MRI: right cerebellar and pontine infarcts • CTA: right vertebral artery stenosis	• Elevated ESR • Positive ANA • Positive anti-ds-DNA • Positive ASMA • C3 and C4 protein depression	• Treatment not reported • Follow-up not reported
37 y/o woman [12]	• Acute dizziness, right hemiparesis, horizontal nystagmus • Previously misdiagnosed as Multiple Sclerosis	• MRI: multiple cerebellar and pontine ischemic lesions • CTA: left vertebral artery stenosis, hypoplastic right vertebral artery	• LE cells absent • Normal ESR • Positive anti-ds-DNA • C3 and C4 protein depression	• Treatment not reported • Follow-up not reported

(*continued on next page*)

Table 1 (*continued*)

Demographics relevant past history	Initial ischemic cerebrovascular event	Neuroimaging findings	Laboratory investigations	Treatment, follow-up & neurological outcome
27 y/o woman, 5th month of pregnancy [13]	• Acute aphasia, right hemiparesis, right hypesthesia, right homonymous field defect	• Catheter arteriogram: left internal carotid artery occlusion • CT: not applicable	• Proteinuria • Elevated ESR • Positive LE cells	• Treatment unknown • Follow-up unknown
37 y/o man, history of rheumatoid arthritis and hypothyroidism, mother's history of SLE	• Acute dizziness, left hemiataxia and gait ataxia	• MRI: acute ischemic lesion in the territory of left SCA • CTA: no large vessel occlusive disease	• Elevated APTT • Thrombocytopenia, followed by pancytopenia • Positive anti-ds-DNA • Positive anti-SSA • Positive lupus anticoagulant • Elevated ESR	• High-dose IV corticosteroids • Hydroxychloroquine • IV heparin, followed by acenocoumarol • No further events for the next 12 months

Anti-Sm antibody: anti-Smith antibody, ASMA: anti-smooth muscle antibody, APTT: activated partial thromboplastin time, CT: computerized tomography, CTA: CT angiography, ESR: erythrocyte sedimentation rate, IV: intravenous, FANA: fluorescent antinuclear antibody, LE cells: lupus erythematosus cell, MCA: middle cerebral artery, MRI: magnetic resonance imaging, PCA: posterior cerebral artery, TIA: transient ischemic attack, VDRL: venereal disease research laboratory, WR: Wassermann reaction.

dissection, hypercoagulable states and rarely cerebral vasculitis [1,4]. Large vessel occlusion due to atherosclerosis is unusual in the early stages of the disease, where cardioembolism, hypercoagulable states and arterial dissection are the often diagnosed etiologies [11].

The majority of the patients (7 of 11), had ischemic infarcts in the distribution of the vertebrobasilar system, with the pons being the most frequently affected structure. In only three cases the pathogenic mechanism could be suspected (two cases compatible with dissection and one with inflammatory lesion), but eventually in none of them it was clearly identified. Nevertheless, all patients were found to have at least one auto-antibody, suggesting an underlying inflammatory or hypercoagulable state. Arterial stenoses were found in four cases, and arterial occlusions in two. In our case, the patient was investigated thoroughly, and, although cardiogenic embolism and vertebral artery dissection were the conditions that were initially considered in such a clinical scenario, the diagnostic investigations revealed no sign of either, and the event was attributed to a hypercoagulable state induced by highly active SLE. No other findings, such as large vessel atherosclerosis, cerebral aneurysm, vasculitis, systemic premature atherosclerosis, dyslipidemia, hypertension, or diabetes mellitus were discovered.

The treatment choices were reported in only three of the cases we reviewed. In all of them, immunosuppressant therapy (either with oral prednisolone or IV cyclophosphamide) was used, in combination with oral anticoagulants or antiplatelet agent. For our patient we also elected to utilize immunosuppressant therapy (high dose IV corticosteroids, followed by oral prednisolone), hydroxycholoquine, and anticoagulation (IV heparin, followed by acenocoumarol). We feel that the combination of immunosuppressant and anticoagulation therapy is important for early secondary stroke prevention, because of the high activity of SLE and the high frequency of stroke recurrence after the initial vascular event.

Follow up data were scarcely documented in the literature cases were reviewed, and at present the occurrence of ischemic stroke as first manifestation of SLE cannot be correlated with specific outcomes, especially the risk of a second stroke, myocardial infarction or death. Our patient showed no abnormal signs at 3-months and 12-months, indicating fully recovery.

5. Conclusions

The diagnosis of SLE is always a challenge due to the wide variety of its manifestations. The occurrence of ischemic stroke, primarily in the vertebrobasilar territory among young patients, especially women, should always raise suspicion for underlying SLE, and prompt diagnostic investigations to confirm or exclude its presence.

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