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WILEY Haemophilia

LETTER TO THE EDITOR

# Cerebrovascular diseases in hemophiliacs: A real, but underestimated risk

Ischaemic heart disease and ischaemic stroke are the most important causes of death in the general population, especially in developed countries. Usually, patients with haemophilia (PWH) are considered at low risk for these events because of their hypocoagulable state, but recent data revealed an unexpected risk of cardio- and cerebrovascular diseases in this population[1,2] as well. However, only a few cases of ischaemic strokes have been reported in PWH, though without detailed description. An occlusion of the sylvian artery in a patient with severe haemophilia B was cited by Luscher.[3] Six cases of cerebral thrombosis have been recorded by Girolami et al.,[4] and four of them were ischaemic events. Wang et al.[2] collected data on 1054 PWH from 1997 to 2010 using a Taiwanese registry, finding 26 ischaemic strokes, a proportion comparable with those of normal subjects, whereas haemorrhagic stroke was seven times higher in the PWH. In this registry, it was also proved that the risk factors for atherosclerosis development, the first cause of thromboembolic injuries, had the same prevalence in both groups except for obesity, which was more frequent in PWH. Conversely, a very low estimated incidence was reported by Bezzina et al.[5] in their data collection on 2569 patients with haemophilia A, haemophilia B and von Willebrand disease from 52 centres in North and South America and in Europe. Over the 4.5-year follow-up period, only four strokes were recorded. Again, data differed in a population of more than 700 PWH from the Netherlands and United Kingdom,[6] and the predicted 10-year risk of fatal myocardial infarction or stroke was significantly higher than in the general population, while in their 5-year cross-sectional study conducted in the USA on PWH >35 years, Sharathkumar et al.[7] reported seven ischaemic strokes in PWH A and B and showed that these patients had twice the lifetime prevalence of coronary artery disease, stroke and myocardial infarction compared to Caucasian men overall. To date, there are no specific guidelines on the management of cerebral ischaemic events in PWH. Only recommendations to reduce the traditional risk factors, like hypertension, obesity and hyperlipidemia, or based on treatment of atrial fibrillation (AF) to prevent cerebrovascular diseases were reported. Recently, the "Consensus Review of the Treatment of Cardiovascular Disease in People with Hemophilia A and B"[8] recommended algorithm for the management of AF in older PWH without inhibitors in order to reduce embolic events. The most important determinant of AF management in PWH is the baseline level of FVIII or FIX. People with severe haemophilia are considered candidates for thromboprophylaxis only if previously treated on prophylaxis with factor concentrate. The decision to initiate antithrombotic therapy with low-dose aspirin or oral anticoagulants is further based on the individual projected risk of stroke.

With this background and gaps in knowledge, this letter presents and retrospectively describes three cases of ischaemic stroke that have occurred among the adult PWH treated at our Hemophilia Center in the last 10 years, with special reference to their management and long-term follow-up.

*First patient*: A 45-year-old patient, with severe haemophilia A treated on-demand with recombinant FVIII (rFVIII) and suffering from hypertension, HBV/HCV-related liver disease and allergy to aspirin, was admitted to our hospital due to the sudden onset of dizziness, postural instability, risk of falling towards his left side, nausea, vomiting and diplopia. One hour after admission, the patient presented with left ptosis, left half facial hypoesthesia and dysesthesia to the four limbs. The patient reported that 20 days before, he had intense pain in the left lateral-cervical and retro-neck regions with dysaesthesias to the left half face after neck hyperextension that resolved with NSAIDs intake. EchoColor Doppler TSA showed a pervious right vertebral artery with normal blood flow and signs compatible with vessel dissection, and a pervious left vertebral artery with pre-occlusive flow. A trans-cranial Doppler ultrasound showed an occlusion of the intracranial tract of the left vertebral artery, while a cerebral angio-MRI revealed a recent left lateral bulbar ischaemic stroke involving the inferior cerebellar peduncle in the same region of the posterior inferior cerebellar artery (Wallenberg Syndrome), double dissection of the vertebral arteries and a recent occlusion of the left vertebral artery. A subsequent CT scan performed in this patient showed an intramural haematoma along the course of the right cervical vertebral artery and minor ischaemic injury in the region of the left posterior inferior cerebral artery. No antiplatelet therapies were prescribed. During the first week of hospitalization, the patient was treated with low-dose rFVIII, 20 UI/kg, every other day, reducing the intramural haematoma. Physiokinetic therapy was also prescribed to the patient. After treatment, the patient's postural instability and all the initial symptoms were reduced. Radiological examinations, performed 1 month after the ischaemic episode, showed a good resolution of the left bulbar ischaemic lesion, a complete reabsorption of haematoma and a normal right vertebral artery, while an occlusion of the prebasilar tract of the left vertebral artery was still found. No relapses were reported at long-term follow-up performed over 104 months after stroke.

*Second patient:* A 53-year-old patient with moderate haemophilia A, on-demand treated with rFVIII, smoker and suffering from HCV-related liver disease was admitted to our hospital because of right hemiparesis. A cerebral CT scan was immediately prescribed and a mild enlargement of the subarachnoid spaces related to age was only revealed. An EchoColor Doppler TSA showed eccentric atherosclerotic

  

**TABLE 1** Baseline characteristics of patients, management of ischaemic events and follow-up

| Cases | Age (y) | Haemophilia degree | Haemophilia treatment | Event description | Risk factors for stroke | Pharmacological management | Follow-up (months of follow-up) |
|---|---|---|---|---|---|---|---|
| 01 | 45 | Severe | On-demand | Left-sided bulbar ischaemic, two vertebral arteries dissection, intramural haematoma along the right vertebral artery | Hypertension | Prophylaxis with rFVIII 20 IU/kg in the first week | Intramural haematoma reabsorption, no relapses (104) |
| 02 | 53 | Moderate | On-demand | Corona radiate ischaemic stroke | Smoke | None | No relapses (51) |
| 03 | 77 | Moderate | On-demand | Vertebro-basilar ischaemic stroke | Hypertension, DMII, obesity, smoke | None | No relapses (84) |

plaque at the left carotid bifurcation with stenosis <20%. A subsequent cerebral MRI showed acute ischaemic injury to the left corona radiata, in the region sprayed by perforating branches of the middle cerebral artery. No antiplatelet therapies were performed. The ischaemic injury gradually reduced and the patient completely recovered his motor function. No relapses or other ischaemic events were reported at follow-up over 51 months from the event. The patient died from cancer related to cirrhosis.

*Third patient:* A 77-year-old patient with moderate haemophilia A, on-demand treated with rFVIII, obese, smoker, suffering from arterial hypertension, diabetes, nephrolithiasis and carotid sinus syndrome, was admitted to our hospital due to sudden diplopia, instabilities in the upright position and ambulation, and dysarthria. A cerebral CT scan showed a bilateral hypodensity nucleus-capsular area, related to recent vascular episodes. An EchoColor Doppler TSA showed a stenosis of 40% on the left side and of 30%-40% on the right side. Sclerohypertensive heart disease was found by ECG and echocardiogram. No antiplatelet therapies were prescribed. During hospitalization, diplopia and ambulation slowly improved. A cerebral MRI performed 20 days from the event excluded active ischaemic injuries, showing only tiny gliotic foci of periventricular white matter related to chronic ischaemic vascular injury. No relapses were reported at long-term follow-up over 84 months after the event. The patient refused prophylactic treatment with aspirin, needed because of his several risk factors for cerebral and cardiovascular diseases (Table 1).

To sum up, overall data[9] suggest that mortality related to cardiovascular diseases is lower in PWH than in the general population owing to their baseline hypocoagulable state, but traditional risk factors for atherosclerosis and subsequent cardio- or cerebrovascular diseases are the same in both groups. Obesity related to limited mobility due to haemophilic arthropathy and hypertension appears higher in PWH than in the general population, and hypertension also proved to be the first cause of intracranial haemorrhage in adult haemophiliacs.[10] As recorded in the literature, blood-borne viral infections, often present in PWH, seem to be related to an increased risk of ischaemic episodes,[11] and indeed in our case, two of three patients had had a previous HCV infection. This report showed that ischaemic strokes usually occur in PWH with the same risk factors, symptoms and outcomes as in the general population. In fact, our patients presented common risk factors for atherosclerosis, such as smoke, hypertension, obesity and diabetes, with subsequent elevated risk of ischaemia. Cardio- and cerebrovascular diseases affect especially older people, and now, life expectancy in PWH is similar to that of the general population. Consequently, more and more PWH will suffer from these diseases in the future.

Published consensus statements recommend the reduction of traditional risk factors to prevent ischaemic stroke,[8] while international guidelines recommend using low-dose antithrombotic drugs based on coagulation factor levels to treat PWH in case of acute stroke or as secondary prophylaxis. Our patients were treated with rFVIII only on-demand and had received no replacement therapy in the week before the ischaemic event. Because of the nature of their ischaemic stroke, all these patients had to be treated with low-dose aspirin and prophylactic dose of FVIII concentrate during the acute phase in order to maintain FVIII >5% in plasma. However, after clinical evaluation of each patient assessing the possibility of spontaneous resolution, no antiplatelet therapies were prescribed, and coagulation factor concentrate was infused only in the patient presenting with intramural haematoma. Secondary prophylaxis was not performed due to patient refusal. Periodic visits to the haemophilia centre were planned to evaluate the follow-up of these patients and, if necessary, to set up a subsequent prophylactic treatment with clotting factor and antiplatelets. So far, none of our patients has needed these treatments.

In conclusion, the strength of our letter lies in providing the first detailed description of ischaemic strokes and stroke management as well as in having a long-term follow-up on patients with haemophilia, but it does not allow us to draw definitive conclusions on the treatment of this atherothrombotic disease. More reports are needed to develop standardized strategies for managing stroke in haemophilia.

## DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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