European Journal of Medical Genetics 62 (2019) 103710

Contents lists available at ScienceDirect

European Journal of Medical Genetics

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

Early-onset stroke in two siblings with Neurofibromatosis type 1

Katarina Rukavina[a,b,*], Rudolf Töpper[c], Alexandra Kunze[c], Alexander Hess[d], Markus Glatzel[a], Jose Manuel Valdueza[e], Said Farschtschi[f], Christian Hagel[a]

[a] Institute of Neuropathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[b] Department of Gerontopsychiatry, Asklepios Klinik Nord, Ochsenzoll, Hamburg, Germany
[c] Department of Neurology, Asklepios Klinik Harburg, Hamburg, Germany
[d] Department of Radiology, Asklepios Klinik Harburg, Hamburg, Germany
[e] Department of Neurology, Segeberger Kliniken, Bad Segeberg, Germany
[f] Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

ARTICLE INFO

Keywords:
Neurofibromatosis type 1
Early-onset stroke
NF1 associated cerebral vasculopathy

ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous disorder, characterized by cafe-au-lait macules, benign neurofibromas as well as malignant peripheral nerve sheath tumours, freckling in the axillary or inguinal regions, optic glioma and Lisch nodules (iris hamartomas) and further manifestations like bone deformities etc.

Additionally, NF1 patients are at increased risk of early-onset cerebrovascular diseases, the pathogenesis of which has not been clarified yet.

Here we report the first case of two siblings with NF1 who suffered an acute ischemic stroke.

Professionals treating NF1 patients should be aware of the elevated risk of stroke in this population. Large prospective studies are needed to establish optimal guidelines for diagnosis, monitoring and treatment of cerebrovascular disease in patients suffering from NF1, as well as to achieve a consensus on routine vascular screening in NF1.

1. Introduction

Neurofibromatosis type 1 (NF1), or von Recklinghausen disease, is an autosomal dominant neurocutaneous disorder, caused by mutations in the NF1 gene, located on the long arm of chromosome 17 (17q11.2) (Kaas et al., 2013; Oderich et al., 2007). Over 2600 NF1 mutations have been reported in the Human Gene Mutation Database (HGMD) (Mao et al., 2018). The deficiency in neurofibromin, the protein product of NF1 gene, leads to increased mitogenic signalling and increased cellular proliferation. As a disorder of the neural crest, the disease is characterized by cafe-au-lait macules, benign neurofibromas as well as malignant peripheral nerve sheath tumours, freckling in the axillary or inguinal regions, optic glioma and Lisch nodules (iris hamartomas). Learning disabilities and osseous dysplasia may also occur (Mao et al., 2018).

Additionally, NF1 patients are at increased risk of early-onset cerebrovascular diseases, the pathogenesis of which has not been clarified yet (Friedman et al., 2002).

Several reports have focused on early-onset stroke in NF1 patients. Here we report, to the best of our knowledge, the first case of two siblings (a female aged 39 years and her brother aged 36 years) with NF1 who both suffered an acute ischaemic stroke.

2. Case presentation

2.1. Patient 1

This 39-year-old female affected by a familiar form of NF1 was admitted to our department with the acute onset of rotatory vertigo, dizziness and gait deviation with tendency to fall toward the right side. Upon examination her skin showed the typical stigmata of NF1 including multiple cafe-au-lait spots, subcutaneous neurofibromas and freckling in the axillary and inguinal regions, fulfilling three of the major criteria of NF1 defined by the NIH (Fig. 1a und Fig. 1b). Additionally, the patient had a history of hypertension, currently treated with candesartan. Neurological examination at admission revealed nystagmus to the left side, ptosis of the right eye, dysarthria and dissociated sensory loss. A cranial computed tomography (CCT) scan was normal. Magnetic resonance imaging (MRI) of the brain revealed multiple hyper-intensities on diffusion-weighted imaging (DWI) in both

* Corresponding author. Institute of Neuropathology, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20 251, Hamburg, Germany.
E-mail address: k.krbot@uke.de (K. Rukavina).

https://doi.org/10.1016/j.ejmg.2019.103710
Received 5 December 2018; Received in revised form 16 June 2019; Accepted 28 June 2019
Available online 04 July 2019
1769-7212/

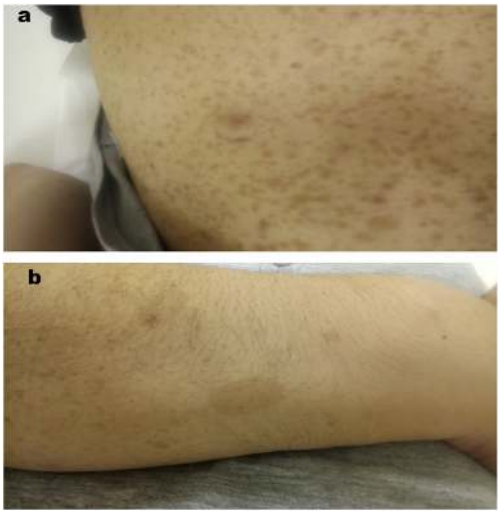

Fig. 1. a and b. Patient 1. Cafe-au-lait macules, subcutaneous neurofibromas and freckling.

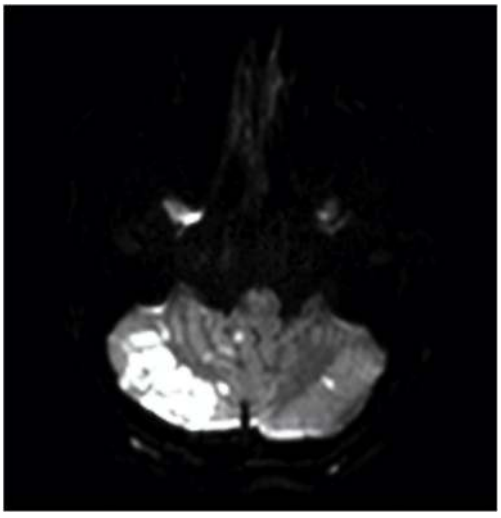

Fig. 2. Axial, diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) for Patient 1. Revealing acute infarcts in both cerebellar hemispheres and in the medulla oblongata.

cerebellar hemispheres and in the medulla oblongata, representing acute infarcts (Fig. 2). Contrast-enhanced magnetic resonance angiography (ce-MRA) and time-of-flight angiography (TOF) showed ectasia of the right vertebral artery in the V4 segment (Fig. 3a and Fig. 3b). Electrocardiography (ECG) displayed sinus rhythm, echocardiography was normal. Laboratory investigations performed for vasculitis (cytoplasmic and perinuclear anti-neutrophil cytoplasmic antibodies (c-ANCA and p-ANCA), anti-myleoperoxidase antibodies and anti-proteinase 3 antibodies) were negative. Laboratory evaluation of risk factors for thrombophilia detected no significant abnormalities (homocysteine 10.5 μmol/L, fibrinogen 470 mg/dl, antithrombin activity 86%, negative anti-cardiolipin antibodies, negative anti-beta-2 gylcoprotein 1 antibodies, coagulation factor VIII 114%, protein C antigen 102%, resistance to activated protein C 3.00, free protein S 85%). Blood lipid levels were elevated (triglicerydes 223 mg/dL, cholesterol 233 mg/dL, LDL-cholesterol 164 mg/dL), but extra- and intracranial duplex sonography did not show any atherosclerotic plaques. The patient was discharged with a low dose oral antiplatelet therapy and simvastatin. During a 4-week intensive rehabilitation program, she recovered completely, and remained without any neurological deficit. MRI performed at four-year follow up did not reveal any acute infarction; the ectasia of

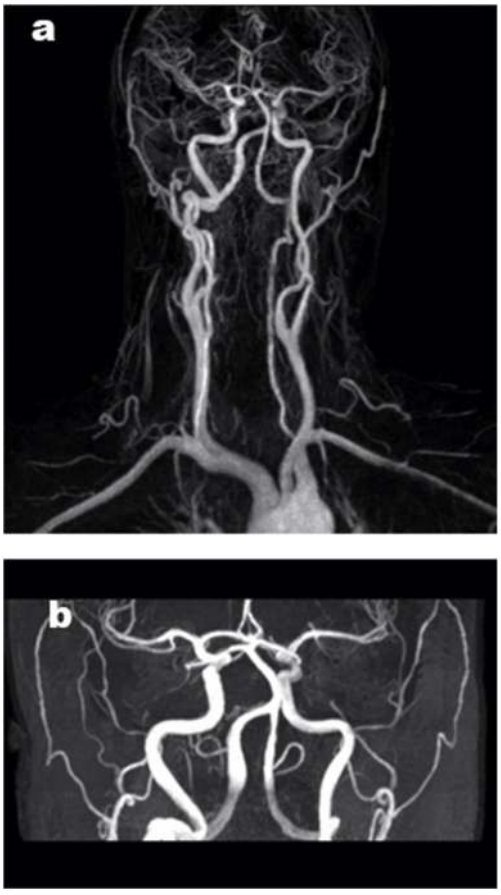

Fig. 3. Patient 1. Contrast-enhanced magnetic resonance angiography (ce-MRA) (a) and time-of-flight angiography (TOF) (b) showing ectasia of the right vertebral artery in the V4 segment.

the right vertebral artery remained unchanged on TOF images.

2.2. Patient 2

This 36-year-old male, the younger brother of patient 1, presented with speech difficulties and a weakness of the left side of the body. The diagnosis of NF1 was made already in childhood, based on clinical findings; cafe-au-lait spots and subcutaneous neurofibromas. At the age of 32, DNA sequencing revealed a previously reported nonsense mutation in exon 4 of the NF1 gene (NM_000267.3:c.441C > A), confirming the diagnosis of NF1 (Zhang et al., 2015). At admission, neurological evaluation revealed a dysarthria, left-sided facial palsy and a left hemiparesis. CCT was normal, but MRI revealed DWI acute infarct of the left lentiform nucleus (Fig. 4.). ce-MRA and TOF demonstrated a hypoplasia of A1 segment of the left anterior cerebral artery (ACA), a common anatomical variant, found in 10% of postmortem examinations (Fig. 5.a and Fig. 5.b). (Makowicz et al., 2013) Extra- and intracranial duplex sonography detected no atherosclerotic plaques (Fig. 6.) ECG documented normal sinus rhythm; echocardiography showed normal ventricular function, with no evidence of patent foramen ovale or cardiac emboli. The blood pressure was not elevated. Vasculitis (c-ANCA and p-ANCA, anti-myleoperoxidase antibodies and anti-proteinase 3 antibodies were negative) and thrombophilia screen (fibrinogen 287 mg/dl, antithrombin activity 96%, negative anti-cardiolipin antibodies, negative anti-beta-2 gylcoprotein 1 antibodies, protein C antigen 120%, resistance to activated protein C 3.04, free protein S 91%) and cerebrospinal fluid (CSF) analysis (< 5 lymphocytes/μL, protein 44.3 mg/dl, glucose 71 mg/dl) were unremarkable. Blood lipid levels were not significantly elevated (triglicerydes 87 mg/dL, cholesterol

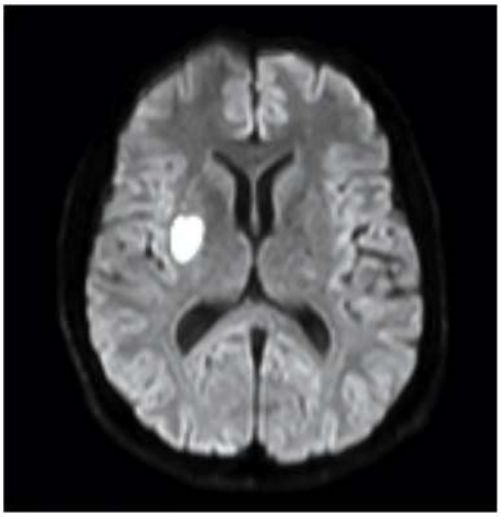

Fig. 4. Patient 2. Acute infarct of the left lentiform nucleus detected on DWI.

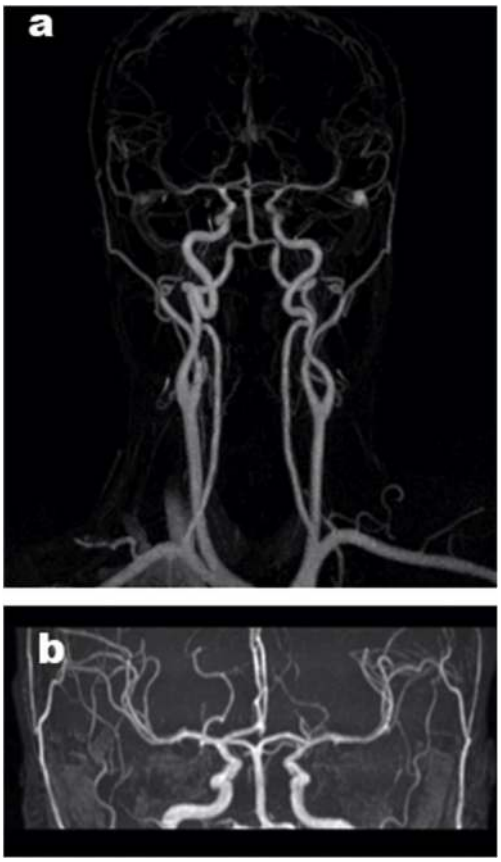

Fig. 5. Patient 2. ce-MRA (a) and TOF (b) demonstrating hypoplasia of A1 segment of the left anterior cerebral artery (ACA).

202 mg/dL, LDL-cholesterol 143 mg/dL). The patient received antiplatelet therapy, and a rehabilitation program was started. On two-years clinical follow up neurological examination revealed a very mild paresis of the left hand, MRI did not show any acute ischaemia. There were no cerebrovascular abnormalities noted in ce-MRA or TOF.

3. Discussion

Early-onset cerebrovascular diseases are significant, but under-recognized complication in NF1 patients. One recent case-control study

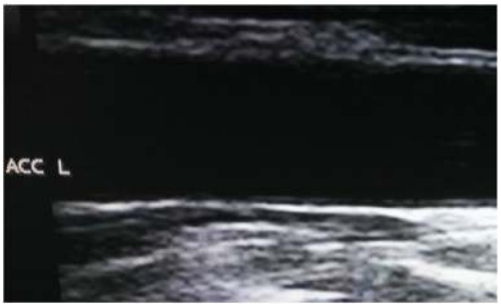

Fig. 6. Extracranial duplex sonography of the left common carotid artery (CCA) for patient 1. No atherosclerotic plaques could be detected.

has shown that, when compared with the general population, NF1 patients who suffer stroke have a significantly younger mean age and are less likely to have common stroke risk factors including diabetes mellitus, atrial fibrillation and atherosclerosis (Terry et al., 2016).

Several large clinical studies have addressed the prevalence of NF1 associated cerebral vasculopathy, with results varying from 2.5% to 15% (Kaas et al., 2013; Cairns and North, 2008; Rea et al., 2009; D'Arco et al., 2014; Rosser et al., 2005) (Table 1). Cerebral vascular abnormalities usually affect the arterial circulation, and include moyamoya arteriopathy, cerebral aneurysms, and stenotic or ectatic cerebral vessels (Friedman et al., 2002; Zhang et al., 2015). Concerning the pathogenesis, neurofibromin is assumed to play the central role (Kaas et al., 2013; Cairns and North, 2008). It is believed that aberrant neurofibromin leads to loss of integrity of the endothelial cell layer and to an abnormal proliferation of smooth muscle cells within the vessel wall, a process analogous to the mechanism leading to formation of multiple neurofibromas (Kaas et al., 2013; Oderich et al., 2007; Cairns and North, 2008). This is especially pronounced in response to mechanical arterial injury; thus, the NF1-associated vasculopathy appears to be acquired, and both progression of existing lesions, and the development of new lesions have been described (Kaas et al., 2013). The proliferation of Schwann cells within the vessel walls is another potential contributor in the pathogenesis of the NF1-associated vasculopathy (Oderich et al., 2007).

Furthermore, NF1 patients are more likely to suffer from hypertension, a major risk factor for stroke and cardiac disease. Essential hypertension is by far the most common form, but NF1 also predisposes to pheochromocytoma and renal artery stenosis, both causing secondary hypertension (Friedman et al., 2002).

Interestingly, haemostasis results in some individuals with NF1 are, reportedly, attenuated, which may possibly contribute to the raised risk of stroke in this population (Favaloro et al., 2004).

Here we present two siblings affected by the familiar form of NF1 who suffered from ischemic stroke at young age. In the first patient, three risk factors for stroke were identified, comprising ectasia of the right vertebral artery in the V4 segment, hypertension and elevated levels of triglyceride and cholesterol. However, acute infarcts in both cerebellar hemispheres and in the medulla oblongata are not entirely explained by hypothesized artery-to-artery embolic events. Moreover, despite the hypertension, hypertriglyceridemia and hypercholesterolemia, extra- and intracranial ultrasound examination revealed normal findings, with no atherosclerotic plaques. Therefore, it is rather unlikely that the stroke in this patient was caused by atherosclerosis.

Interestingly, the second patient showed no cerebrovascular abnormalities, hypertension, or any other common risk factors, underlining the assumption that stroke was likely not to be caused by typical risk factors in the two siblings.

Our study has certain limitations: the availability of clinical data for the NF1 affected mother of our patients was very restricted, and it remains unclear, if she suffered an ischaemic stroke. Furthermore, no exome or whole genome sequencing has been performed in our

Table 1
The prevalence of NF1 associated cerebrovascular abnormalities in large clinical studies.

	NF1 cases (n)	Cerebrovascular abnormalities	
		Patients(n)	Percent(%)
"Cerebrovascular dysplasia in neurofibromatosis type 1" - Cairns and North et al., 2008	144	7	5
"Spectrum and prevalence of vasculopathy in pediatric neurofibromatosis type 1" - Kaas et al., 2013	77	12	15
"Cerebral Arteriopathy in children with neurofibromatosis type 1" - Rea et al., 2009	266	17	6
"Cerebrovascular abnormalities in a population of children with neurofibromatosis type 1" - Rosser et al., 2005	316	8	2,5
"Cerebrovascular stenosis in neurofibromatosis type 1 and utility of magnetic resonance angiography: our experience and literature review" - D'Arco et al., 2014	81	6	7,4

patients; consequently, we cannot exclude that some additional, NF1 independent, genetic factors possibly contributed to predisposition for early onset stroke in our patients.

Nevertheless, our study has important implications. Its novelty lies in the following two aspects: First, although the elevated risk of stroke in NF1 patients is well-acknowledged fact, here we are reporting the first case of two siblings with NF1 who suffered an early-onset acute ischaemic stroke, possibly pointing towards a distinct NF1 phenotype, including cerebrovascular complications (Friedman et al., 2002). Second, large retrospective studies have already reported increased risk of early-onset stroke in patients with NF1; *yet none fully highlights the underlying pathogenic process causing stroke in NF1-patients. Importantly, we* provide evidence that the absence of cerebrovascular abnormalities does not rule out the elevated risk of stroke in NF1 patients, and that the pathophysiological changes leading to the occurrence of acute stroke seem to differ from the common risk factors in the population. In fact, clinical diagnosis of NF1 might be an independent risk factor for stroke, and this might, furthermore, be particularly associated with certain mutations in NF1 gene (Terry et al., 2016). However; the exact pathophysiological mechanism and the natural history of cerebrovascular ischaemia in NF1-patients remain to be highlighted.

The relevant data form this report are hosted at the ClinVar Database, accession number SCV000914193.

4. Conclusion

Professionals involved in the management of NF1 patients should be aware of the elevated risk of stroke in this population, and consider stroke in the differential diagnosis in NF1 patients presenting with new neurological symptoms. There is a high unmet need for large prospective studies to establish optimal guidelines for diagnosis, monitoring and treatment of cerebrovascular disease in patients suffering from NF1, as well as to achieve a consensus on routine vascular screening in NF1.

References

Cairns, A.G., North, K.N., 2008. Cerebrovascular dysplasia in neurofibromatosis type 1. J. Neurol. Neurosurg. Psychiatry 79 (10), 1165–1170.
D'Arco, F., D'Amico, A., Caranci, F., et al., 2014. Cerebrovascular stenosis in neurofibromatosis type 1 and utility of magnetic resonance angiography: our experience and literature review. Radiol. Med. 119 (6), 415–421.
Favaloro, E.J., Zafer, M., Nair, S.C., Hertzberg, M., North, K., 2004 Oct. Evaluation of primary haemostasis in people with neurofibromatosis type 1. Clin. Lab. Haematol. 26 (5), 341–345.
Friedman, J.M., Arbiser, J., Epstein, J.A., et al., 2002. Cardiovascular disease in neurofibromatosis 1: report of the NF1 cardiovascular task force. Genet. Med. 4, 105–111.
Kaas, B., Huisman, T.A., Tekes, A., et al., 2013. Spectrum and prevalence of vasculopathy in pediatric neurofibromatosis type 1. J. Child Neurol. 28, 561–569.
Makowicz, G., Poniatowska, R., Lusawa, M., 2013. Variants of cerebral arteries - anterior circulation. Pol. J. Radiol. 78, 42–47.
Mao, B., Chen, S., Chen, X., et al., 2018. Clinical characteristics and spectrum of NF1 mutations in 12 unrelated Chinese families with neurofibromatosis type 1. BMC Med. Genet. 19 (1), 101.
Oderich, G.S., Sullivan, T.M., Bower, T.C., et al., 2007. Vascular abnormalities in patients with neurofibromatosis syndrome type I: clinical spectrum, management, and results. J. Vasc. Surg. 46, 475–484.
Rea, D., Brandsema, J.F., Armstrong, D., et al., 2009. Cerebral arteriopathy in children with neurofibromatosis type 1. Pediatrics 124 (3), e476–e483.
Rosser, T.L., Vezina, G., Packer, R.J., et al., 2005. Cerebrovascular abnormalities in a population of children with neurofibromatosis type 1. Neurology 64, 553–555.
Terry, A.R., Jordan, J.T., Schwamm, L., et al., 2016. Increased risk of cerebrovascular disease among patients with neurofibromatosis type 1: population-based approach. Stroke 47, 60–65.
Zhang, J., Tong, H., Fu, X., et al., 2015. Molecular characterization of NF1 and neurofibromatosis type 1 genotype-phenotype correlations in a Chinese population. Sci. Rep. 9 (5), 11291.