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LETTER TO THE EDITORS

Evidence for inflammation in Fabry's disease? Headache and muscle involvement responding to corticosteroid and methotrexate treatment

Markus Kraemer[1] · N. Karabul[3] · P. Berlit[1] · A. Rolfs[2]

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Dear Sirs,

We report the case of a 38-year-old female patient who had been diagnosed as lupus erythematosus because of generalized muscle and burning pain combined with slightly elevated C-reactive protein (CRP) and antinuclear antibodies (ANA) 1:640. She was treated with low dose corticosteroids which reduced muscle pain. Twelve years later, Fabry's disease was diagnosed by molecular genetics. Lupus erythematosus and any other co-morbid rheumatologic diseases were falsified retrospectively and prospectively according to international classification criteria [1]. Corticosteroid therapy was stopped, but the pain exacerbated. Four rheumatologic examinations within the next 5 years brought no evidence for a rheumatic disease. Cornea verticillata, multiple angiokeratomas and small fiber neuropathy were found as typical manifestations of Fabry's disease. Detailed neurophysiological studies excluded polyneuropathy of the large fibers. There was no renal or cardiac impairment. MRI of the brain showed no pulvinar sign.

The patient suffered from recurrent cerebral strokes despite an enzyme replacement therapy with Replagal® and Fabrazyme®. Small vessel strokes continued to appear about four to five times per year even with a double antiplatelet therapy. Beside lacunar ischemias, there was one territorial infarction. But repeated trans-esophageal echocardiograms, heart MRI and cardiac monitoring (including the insertable device Reveal XT ICM) revealed no cardiac source for emboli.

Moreover, the patient suffered from recurrent strong headaches which were associated with mild CSF pleocytosis and which responded to short-duration intravenous corticosteroids. In addition to a small fiber neuropathy with burning and stinging sensations, the patient described ubiquitous and heavy muscle pain. She had slightly elevated ANA antibodies 1:640 and a permanent slightly increased CRP up to 3–5 mg/dl (standard value <0.5 mg/dl). A muscle MRI showed distinct muscle edema (see Fig. 1a). A muscle biopsy from this region failed to show muscle pathology, especially no signs for myositis or vasculitis. Electron microscopy did not detect deposits of Gb-3.

Stroke frequency, headaches and muscle pain remained therapy resistant despite treatment attempts with amitriptyline, duloxetine, pregabalin, gabapentin, remergil, opioids and enzyme replacement therapy for 5 years. Only the burning and stinging sensations improved with therapy. Moreover, the patient experienced deafness and tinnitus.

Due to the patient's experience of pain release with corticoids when she was misdiagnosed as lupus, and because of the elevated ANA- and CRP-levels and CSF pleocytosis combined with edema in muscle MRI, we started a therapy attempt with corticosteroids 5 mg daily and methotrexate 20 mg weekly. As a consequence, muscle pain and headache disappeared completely. An additional muscle MRI demonstrated resolution of the edematous changes we found previously (see Fig. 1b). The CRP levels normalized, and no new strokes occurred after initiation of the immunosuppressive treatment with corticosteroids and methotrexate. Improvement of stroke frequency has to be interpreted with caution because it could be by chance.

✉ Markus Kraemer
markus.kraemer@krupp-krankenhaus.de

[1] Department of Neurology, Alfried Krupp Hospital, Alfried-Krupp-Str. 21, 45117 Essen, Germany

[2] Albrecht Kossel Institute, University Clinic of Rostock, Gehlsheimer Str. 20, 18147 Rostock, Germany

[3] Child's Neurology Clinic, University of Bochum, Alexandrinenstrasse 5, 44791 Bochum, Germany

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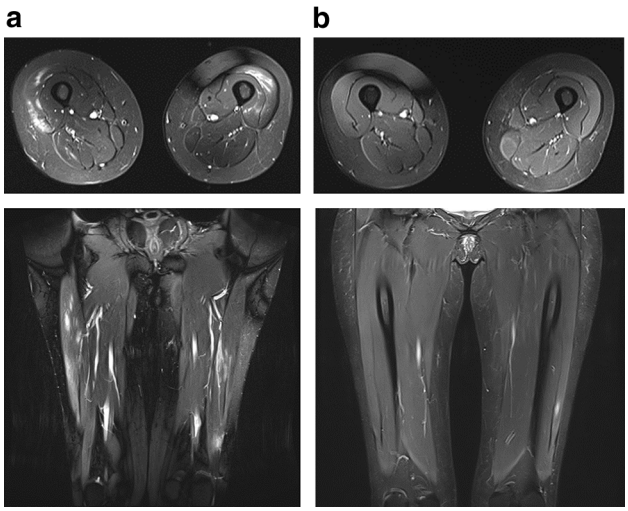

Fig. 1 **a** Muscle MRI before treatment with corticosteroids and methrotexate. **b** Muscle MRI under a treatment with corticosteroids and methrotexate

This case illustrates, that in addition to the deposition of lyso-gb3 secondary inflammatory mechanisms may play an important role in the pathophysiology of symptoms in Fabry's disease. The c.-174G>C polymorphism in the IL6 gene, which is known to be correlated with a worse outcome in Fabry's disease [2], was not found in this patient. Nevertheless, we suspect an interleukin associated necrosis of the media vessel lamina with consecutive vasculitis. Repeated neurological and rheumatologic clarifications in several hospitals did not lead to other or additional diagnoses beside Fabry's disease combined with unspecific inflammatory signs.

Furthermore, this case supports other research suggesting an immunological component in Fabry's disease. Kikumoto et al. reported similar cases with persistent inflammation in Fabry's disease [3]. De Francesco et al. and Biancini et al. showed proinflammatory cytosine production profiles in Fabry's disease [4, 5]. Also other new research supports the role of inflammation in Fabry's disease [6–8]. Perhaps researchers can learn from another rare disease which might have parallel disease mechanism: In amyloid beta associated angiitis (ABRA) inflammation seems to represent an autoimmune response to vascular β-amyloid deposits which might be comparable to Gb3-associated inflammation mechanism in Fabry's disease [9, 10].

However, further research is needed before an immunosuppressive therapy can be recommended generally in Fabry's disease. However, our case demonstrated that inflammation might be an important factor in symptom persistence despite enzyme replacement therapy.

Compliance with ethical standards

Conflicts of interest Markus Kraemer received research grants from Novartis and Merck Serono and travel/accommodations/meeting expenses or lecture honoraria by Bayer Schering, Biogen Idec, Merck Serono, Novartis, Teva and Shire Germany. Nesrin Karabul received research grants and travel/accommodations/meeting expenses or lecture honoraria by Genzyme, Shire and Amicus. Peter Berlit received honoraria for lectures or travel/accommodations/meeting expenses by Bayer Schering, Biogen Idec, Merck Serono, MSD, and Novartis. Arndt Rolfs received research grants and travel/accommodations/meeting expenses or lecture honoraria by Genzyme, Shire and Amicus.

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