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SEVERE CARDIAC FAILURE IN A PATIENT WITH MULTIPLE SCLEROSIS FOLLOWING LOW-DOSE MITOXANTRONE TREATMENT

The synthetic antineoplastic anthracenedione mitoxantrone (MiTX) is well established as second-line treatment for worsening relapsing-remitting (RR) and secondary chronic progressive (SP) multiple sclerosis (MS).¹ MiTX has a dose-related cardiotoxic potential which limits the cumulative lifetime dose in MS to 140 mg/m². Up to a cumulative dose of 100 mg/m², MiTX treatment is considered relatively safe.^{1,2} The risk of MiTX-induced congestive heart failure increases with the cumulative dose, previous treatment with anthracyclines, preexisting cardiovascular disease, and age. The development of acute severe heart failure shortly after initiation of MiTX treatment in MS has not been reported so far. Recently, the individual susceptibility to MiTX-induced side effects has been linked to naturally occurring genetic variations in ATP binding cassette (ABC) drug transporters.³

Case presentation. The diagnosis of RRMS was established in an otherwise healthy 26-year-old woman in 2003. In November 2005 and February 2006, she received 2 doses of MiTX (12 mg/m² body surface area per infusion) due to high disease activity without any immediate periprocedural complications. Before application of the first and second dose, physical examination, echocardiography, and electrocardiogram were normal. Two months after the second pulse, the patient rapidly developed a severe acute biventricular cardiac failure with a left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) of 10%, severe pulmonary edema, aspiration pneumonia, and hepatic and renal failure. After stabilization by artificial ventilation, catecholamine substitution, and hemofiltration, cardiac function subsequently improved, with LVEF and RVEF both at 60%. A myocardial biopsy performed 3 weeks after onset showed substantial interstitial edema, increase of fatty tissue, and diffuse perimysial and interstitial fibrosis with immunohistochemical reactivity against collagen subtypes III and IV, consistent with anthracycline-mediated toxic cardiomyopathy,^{4,5} but no lymphocytic infiltrations, which strongly argued

against myocarditis (figure). Thus, biopsy findings were in agreement with a toxic cardiomyopathy which, in the absence of any further toxic substances, could only be attributed to the MiTX treatment. The patient recovered completely and follow-up echocardiographies were normal. Screening for genetic variation associated with altered drug deposition of MiTX³ revealed variant alleles in 2 loci of the *ABCB1* drug transporter gene (rs1045642 [3435C>T, TT genotype], rs2032582 [2677C>A, AA genotype]) and a variant allele in one locus in the *ABCG2* gene (rs2231142 [Q141K, i.e., G>T, TT genotype]).

Discussion. In our patient, a clinically completely reversible toxic cardiomyopathy was diagnosed based on the histology of the ventricular biopsy. Lack of significant inflammatory infiltration or granuloma argued against an inflammatory or autoimmune-mediated etiology. Normal physical, electrocardiographic, and echocardiographic examinations before MiTX treatment and the fact that she had not taken any cardiotoxic substances previously strongly argued against preexisting cardiac disease. Thus, by exclusion, the cardiomyopathy is probably attributable to MiTX treatment.

Congestive heart failure in patients with MS is considered a dose-related and delayed complication of MiTX beyond a cumulative dose of 100 mg/m², in particular in patients with additional cardiac risk factors. To date, there is an ongoing debate regarding whether a safe cumulative MiTX dose exists. Several studies including a recent metaanalysis have conclusively demonstrated that treatment up to a cumulative dose of 100 mg/m² is safe.^{2,6} On the other hand, an asymptomatic drop of LVEF below 50% and/or of more than 10% from baseline value was observed in MiTX-treated patients with MS below a cumulative dose of 100 mg/m²,^{2,7} suggesting that subclinical cardiotoxicity already occurs below a dose of 100 mg/m². The development of toxic cardiomyopathy shortly after a second course of MiTX reported here is the first description of clinically relevant cardiotoxicity in a young patient without preexisting cardiac disease or preceding cardiotoxic treatment. In patients with MS carrying a combination of *ABCG2*/*ABCB1* SNPs, in vitro MiTX-efflux has been

Figure Mitoxantrone-induced toxic cardiomyopathy

(A) Hematoxylin-eosin staining of right ventricular myocardial tissue showing severe interstitial edema, mild hypertrophy with cardiomyocytes, and nuclei of variable size (arrows). (B) Staining of collagen III showing diffuse interstitial fibrosis with transition into scarring (arrows). (C) Staining of collagen IV showing both generalized perimysial and perivascular (arrows) fibrosis. Myocytolysis, specific infiltration, ischemic demarcation, endothelial hypertrophy, or obstructions of vessel lumina are not present. In consideration of the age, the proportion of connective tissue (13% vol, normal <9% vol) is pathologically increased. Magnification $\times 20$.

reported to be lower than in wild-type individuals, leading to intracellular MiTX accumulation and cell death.³ Although it remains hypothetical in a single patient, the abnormal cardiotoxicity of MiTX in our

patient might have been favored by increased MiTX exposure due to the combination of three SNPs in the *ABCB1* and *ABCG2* genes. Our report demonstrates that even a normal LVEF in a pretreatment echocardiography is not sufficient to exclude severe cardiologic complications. In sum, the almost fatal complication reported here challenges the assumption that MiTX can be considered safe regarding cardiac side effects below a certain threshold dose. Future prospective studies will clarify the impact of genetic variations in the ABC drug transporters on the MiTX safety profile and help to identify patients at risk for MiTX-mediated side effects.

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A PATIENT WITH EPISODIC ATAXIA AND PARAMYOTONIA CONGENITA DUE TO MUTATIONS IN *KCNA1* AND *SCN4A*

Channelopathies are mendelian disorders arising from mutations in genes that encode ion channel subunits.¹ Mutations in *SCN4A*, which encodes the α -subunit of the muscle sodium channel Nav1.4, underlie paramyotonia congenita (PMC),² while mutations in *KCNA1*, which encodes the potassium channel subunit Kv1.1, cause episodic ataxia type 1 (EA1) and isolated myokymia.³ We describe the clinical, genetic, and functional expression studies in an unusual patient who harbors mutations in both *SCN4A* and *KCNA1* and report that sodium channel dysfunction dominates the phenotype.

Case history. A 34-year-old woman had a lifelong history of muscle cramps and weakness affecting upper and lower limbs. Symptoms were exacerbated by exercise and cold weather, which induced both muscle stiffness and difficulty releasing her grip. Her father, paternal uncle, and second son are similarly affected. Examination demonstrated weakness of intrinsic hand muscles (Medical Research Council 4/5) with paradoxical myotonia of hand grip and eye closure.

Neurophysiology confirmed a diagnosis of PMC, with a cooling test showing a rapid decrement in amplitude and area, which did not recover with rewarming. A McManis test was positive, showing a >40% decrement in compound muscle action potential (CMAP) during exercise with recovery during the prolonged rest period. Unexpectedly, needle EMG demonstrated sustained doublets, triplets, and multiplets interspersed with the myotonic discharges in the right abductor digiti minimi, biceps, tibialis anterior, and thoracic paraspinals (figure A). Because generalized myokymic discharges are not a recognized feature of PMC, this prompted further direct questioning about her symptoms. She reported that since the age of 16, she had experienced brief attacks of slurred speech and unsteadiness lasting seconds to minutes. Emotional stress was a trigger for these episodes, which the patient dismissed as “panic attacks.” Reexamination on a separate occasion confirmed fine lateral movements of her fingers suggestive of myokymia. This raised the possibility of a clinical

diagnosis of EA1 and PMC, with the latter dominating the phenotype.

Genetic results. Sequencing *SCN4A* revealed the functionally characterized point mutation T1313M, confirming the diagnosis of PMC. T1313M segregated with affected members in her family. Sequencing *KCNA1* identified a heterozygous G to A change at nucleotide position 895, which predicts a valine to isoleucine substitution at the highly conserved codon 299 in the fourth transmembrane segment of the α -subunit. The V299I mutation has not been reported previously and was absent in a large panel of over 200 control chromosomes. The mutation was absent in the patient’s father. It was not possible to obtain DNA from the mother but she did not have EA1 clinically.

Electrophysiology. The V299I mutation conferred a significant positive shift in the $V_{1/2Max}$ of the voltage dependence of activation of Kv1.1 channels (figure, B and C) when expressed alone (V299I: +26.9 mV, $p < 0.0001$) and also when coexpressed with WT channels (coexpression: +18.8 mV $p < 0.0001$; WT alone: -35.3 ± 0.07 , $n = 5$). Cells expressing mutant V299I channels also had markedly reduced maximal potassium current density, as measured from tail currents, compared with cells expressing WT (V299I: 19.3 ± 3.5 pA/pF, $n = 5$; WT: 47.2 ± 3.4 pA/pF, $n = 5$, $p = 0.0005$) (e-Methods on the *Neurology*® Web site at www.neurology.org). When V299I and WT subunits were coexpressed, the current density was similar to V299I alone (figure, D), and significantly lower than WT alone (23.6 ± 3.9 pA/pF, $n = 5$, $p = 0.002$). These findings are consistent with a dominant-negative effect of the mutation.

Discussion. This patient has 2 genetically confirmed diagnoses: PMC and EA1. Although some EA1 mutations cause subtle effects on Kv1.1 function,⁴ the new mutation identified here caused moderately severe loss of function. We have previously reported an imperfect correlation between the decrease in current density and clinical severity of different EA1 mutations.⁵ In this patient, despite quite a severe loss of

Supplemental data at
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(A) Myokymic discharges intermixed with myotonic discharges. (B) Representative current traces of HEK cells expressing Kv1.1 WT, WT:V299I, and V299I obtained by applying a voltage step from a holding potential of -80 mV to 0 mV. Low potassium internal solution (in mM: KCl, 2.5; NaCl, 140; HEPES, 10; and EGTA, 10, pH = 7.3) was used to generate tail currents for assessing current density (see e-Methods). (C) Normalized voltage dependence of activation for cell expressing WT, mutant V299I, and WT: V299I ($n = 5$ for each). Tail currents were sampled 1 msec after return to -80 mV. Error bars are SEM. Inset: Peak potassium currents from representative cells expressing WT, V299I, and WT: V299I. (D) Maximum tail current density measured at +60 mV for WT, V299I, and WT: V299I. Error bars are SEM.

Kv1.1 function, the attacks were mild and the PMC symptoms dominated the clinical picture.

EA1 patients do not always complain of unsteadiness or imbalance but rather dizziness or anxiety. It is important to recognize the varied nature of patient descriptions in order to avoid missing the diagnosis of EA1. The coexistence of two ion channelopathies in this patient raises the possibility of interplay. Interaction between ion channel genes has been studied by combining two epilepsy-associated channel mutations in mice, which resulted in negation of the effects of each.⁶ Here, one might predict that the myokymia would trigger muscle myotonia through repetitive firing and exacerbate the muscle symp-

toms. However, the PMC phenotype was no worse than in other patients with the T1313M mutation alone.⁷ The mechanisms of possible interactions between these 2 mutant channels are likely to be complex. In this double mutant case, PMC was the dominant clinical phenotype.

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