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LETTER TO THE EDITORS

Treatment of SPG5 with cholesterol-lowering drugs

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Dear Sirs,

Spastic paraplegia type 5 (SPG5) is an autosomal recessive hereditary spastic paraparesis (HSP) associated with pure or complicated phenotypes and mutations in *CYP7B1* [1] causing an impairment of the alternative pathway of bile acid synthesis with marked accumulation of 27-hydroxycholesterol (27OHC) in plasma and cerebrospinal fluid [2]. Since brain 27OHC has an extracerebral origin [3], cholesterol-lowering drugs might prevent neurological impairment in SPG5 by reducing circulating 27OHC, which is derived from cholesterol.

We previously reported a nine-month follow-up in two ambulant siblings harboring mutations in SPG5/*CYP7B1* [4]. At that time, we evaluated the effects of statin therapy in one of the two cases (patient 1) and observed moderate serum 27OHC reduction. Here, we present a 24-month follow-up in patient 1, treated with simvastatin and ezetimibe, and a 12-month follow-up in patient 2, treated with ezetimibe alone.

Clinical details, laboratory and instrumental findings, and molecular data in the two patients have been described elsewhere [4]. In the present study, both subjects underwent neurological evaluation including Spastic Paraplegia Rating Scale (SPRS) and Modified Rankin Scale (MRS) clinical scoring, routine blood tests, cholesterol and 27OHC determinations every 3 months, and instrumental follow-up including motor evoked potentials (MEPs), conventional brain magnetic resonance imaging (MRI), and MR spectroscopy every 6 months.

Patient 1 received different oral doses of simvastatin (from 20 to 60 mg/day) during the first 12 months, and then oral ezetimibe 10 mg/day was added to simvastatin 40 mg/day for 12 months. Treatments were well tolerated. Serum 27OHC concentration progressively decreased under treatment with simvastatin either alone (reduction ranged from 10 to 45 % compared to baseline) or when in combination with ezetimibe (55 % decrease compared to baseline), and cholesterol tended to decrease in parallel with 27OHC (Fig. 1a). Association of simvastatin and ezetimibe was more effective in reducing 27OHC than the increase of simvastatin dosage up to 60 mg/day. No changes of neurological disability as well as brain MRI and spectroscopic pattern were observed. MEPs revealed a trend toward improvement or stabilization of central motor conduction times (CMCTs).

Patient 2, who had not tolerated simvastatin because of cramps and marked hyperCKemia [4], received ezetimibe 10 mg/day for 12 months, and tolerated well this therapy. We observed a persistent decrease of serum 27OHC values (38–50 % reduction compared to baseline), whereas cholesterol levels initially decreased and then returned to baseline (Fig. 1b). Alike his sister, SPRS and MRS scores as well as brain MRI and spectroscopy were unchanged. MEPs showed substantially stable CMCTs values over time.

Since chenodeoxycholic acid (CDCA) has been reported to be beneficial in a child with liver disease associated with a missense variant in *CYP7B1* [5], we added oral CDCA

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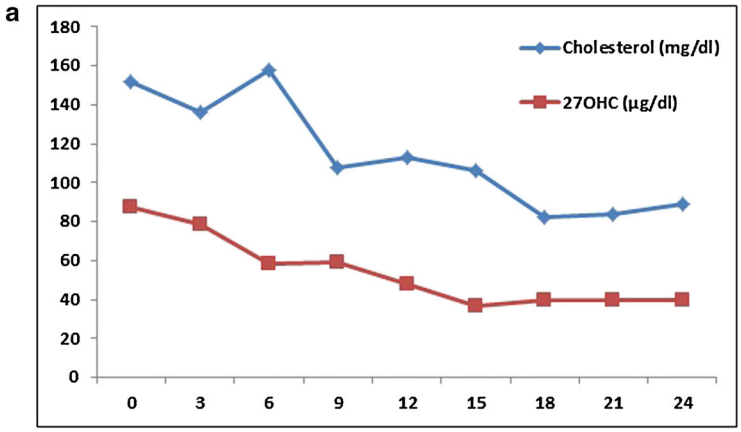
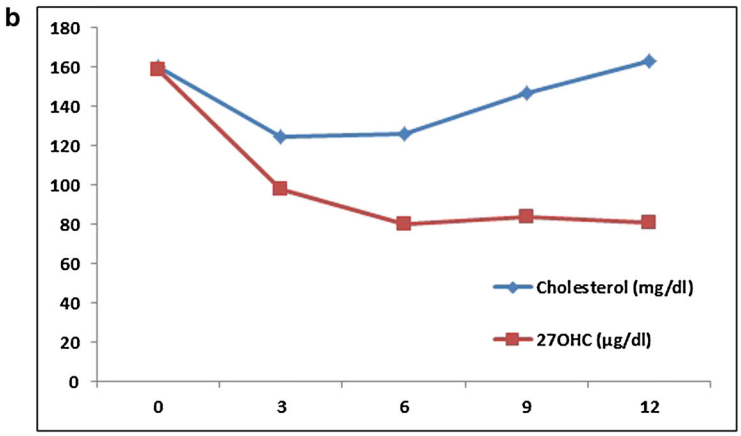


Baseline	No treatment
Month 3	Simvastatin 20 mg
Month 6	Simvastatin 40 mg
Month 9	Simvastatin 60 mg
Month 12	Simvastatin 40 mg
Month 15	Simvastatin 40 mg + Ezetimibe 10 mg
Month 18	Simvastatin 40 mg + Ezetimibe 10 mg
Month 21	Simvastatin 40 mg + Ezetimibe 10 mg
Month 24	Simvastatin 40 mg + Ezetimibe 10 mg



Baseline	No treatment
Month 3	Ezetimibe 10 mg
Month 6	Ezetimibe 10 mg
Month 9	Ezetimibe 10 mg
Month 12	Ezetimibe 10 mg

Fig. 1 **a** Serum cholesterol (mg/dl) and serum 27OHC (µg/dl) levels over a 24-month follow-up period in patient 1. **b** Serum cholesterol (mg/dl) and serum 27OHC (µg/dl) levels over a 12-month follow-up period in patient 2. Normal values: cholesterol 130–200 mg/dl; 27OHC 16 ± 3 µg/dl

500 mg/day to the therapy of our patients. However, CDCA was discontinued after a month due to lack of 27OHC level variation and significant side effects (marked elevation of liver enzymes in patient 1 and diarrhea in patient 2), which disappeared upon drug withdrawal.

In our patients, long-term administration of cholesterol-lowering drugs reduced serum levels of 27OHC by about 50 %, in line with what was expected [2]. Although 27OHC never normalized, we achieved a marked decrease, without loss of biochemical effectiveness over time. Clinical stability was observed at follow-up in both patients, and repeated neurophysiological and imaging examinations did not reveal disease progression.

Even if further studies are needed to prove that 27OHC is the "bad guy" in SPG5 pathogenesis, we think that administration of cholesterol-lowering drugs should be considered in HSP patients harboring *CYP7B1* mutations. Not only HMG-CoA reductase inhibitors but also ezetimibe might be attempted, especially when statins are not tolerated, and combination therapy could also be given. However, more clinical meaningful endpoints should be defined before embarking in double-blind, placebo-controlled clinical trials assessing the efficacy of cholesterol-lowering drugs in SPG5. On the other hand, and based also on our own experience with multiple therapy in two sibs, we cannot draw firm conclusions on efficacy of CDCA in reducing 27OHC in adult *CYP7B1*-mutated patients.

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Compliance with ethical standards

Conflicts of interest We declare that we have no conflicts of interest.

Funding We declare no funding.

Ethical standard This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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