Case report

Eosinophilic myositis in calpainopathy: Could immunosuppression of the eosinophilic myositis alter the early natural course of the dystrophic disease?

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ABSTRACT

An 11-year-old girl with a calpain-3 gene (CAPN-3) mutation and eosinophilic myositis on muscle biopsy had high serum CK levels and eosinophil counts which showed spontaneous fluctuations. After commencement of immunosuppressive therapy reciprocal changes occurred in response to alterations in doses of the medications. Subacutely evolving and spreading muscle weakness developed during tapering of the immunosuppressive medications.

These observations suggest that either the occurrence of eosinophilic myositis or the withdrawal of the immunosuppressive treatment may have accelerated the clinical course of the calpainopathy in this case. The positive effect of immunosuppressive therapy might have implications for the management of calpainopathy with an inflammatory component.

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1. Introduction

Limb girdle muscular dystrophy type 2A (LGMD 2A; OMIM 253600) is reported as being the most prevalent form of autosomal recessively inherited muscular dystrophy in some populations, and is caused by mutations in the gene encoding calpain-3 (CAPN-3; OMIM 114240) [1,2].

It is now well-recognized that the dystrophic process can be accompanied by inflammatory changes in muscle tissue which is thought to be due to a non-specific immune response [3]. Some patients with LGMD 2B and 2I show inflammation of this type and LGMD 2I may respond to corticosteroid therapy [4,5].

Recently, a subset of patients with LGMD 2A have been reported to have a form of “eosinophilic myositis” [6,7]. It is not known why calpain-3 deficiency causes eosinophilic myositis and it is unclear whether the “myositis” in such cases has an aggravating effect on the underlying dystrophic process.

We report a patient with this rare combination of eosinophilic myositis with a CAPN-3 mutation in whom serum CK levels and eosinophil counts showed substantial reciprocal changes during immunosuppressive drug dosing, and cessation of this therapy was associated with a striking clinical deterioration.

2. Case report

An 11-year-old girl was coincidentally found to have a high serum CK level (>7150 IU/L, N: <170 IU/L) during a hepatitis-A infection in March 2006 which resolved by July 2006.

She was followed up in another institution and denied any muscle weakness or pain at that time, claiming that she was competitive in doing even skipping-rope exercises. Repeatedly checked CK levels thereafter ranged between 3749 and 8931 IU/L until January 2007 (Fig. 1). The first motor examination at this time revealed only some tiring after performing four squats without any reported muscle weakness. She then had a muscle biopsy which disclosed variation in fibre size, necrosis, myophagocytosis and regeneration. Prominent inflammatory infiltrates, composed mainly of eosinophils and a few lymphocytes within fibres and in the endomysium, accompanied these changes (Fig. 2). There was no evidence of parasitic infection or vasculitis. Immunocytochemistry for dystrophin, sarcoglycans, merosin and dysferlin was normal. A diagnosis of eosinophilic polymyositis was made. Her blood chemistry, haematology and rheumatology tests were normal except for eosinophil count which was 910/mcL (N: 0–350 mcL).

Prednisolone (PRD) 50 mg/day and azathioprine (AZA) 50 mg/day were instituted in March 2007 after which the tiredness and fatigue were claimed to have improved. Serum CK gradually decreased from 7430 IU/L and reached its lowest follow-up level, 644 IU/L in May 2007. The professed clinical improvement and significant decrease in the CK levels prompted the first physician to
attempt lowering the doses of the medications. Several attempts resulted in returning back to first therapeutic dose as the CK levels, as well as the eosinophil counts and symptoms of dermatitis fluctuated reciprocally with changes in the doses of medications (Fig. 1). Methotrexate (MTX) 15 mg/week was added in May 2007. She was first seen by one of the authors (P.S.) at the end of June 2007. This was when she started feeling slightly “heavy”, during the termination of the medications. She had iatrogenic Cushing’s syndrome. Her muscle strength was normal on the Medical Research Council (MRC) scale except for 4+/5 in iliopsoas and hip adductor muscles, both of which were tested against gravity. There was questionable gastrocnemius hypertrophy. As the direct sequencing of exons of the \( \text{CAPN}-3 \) gene in the patient revealed a homozygous, common disease causing missense \( c.145C > T \) (p.Arg49Cys) mutation in exon 1, the immunosuppressive medication doses continued to be tapered and are then ceased. The CK level rose to 10118 IU/L soon after cessation of the medications and remained high thereafter. Muscle testing by the same neurologist 2 months after stopping the medications showed that strength had dropped to 2/5 in the hip adductors which were tested against gravity again, and was 4/5 in iliopsoas, gluteus maximus, hip abductor and hamstring muscles, 4+/5 in deltoid, biceps and triceps muscles and 5/5 in others. She also had a flare of atopic dermatitis from which she had suffered since an early age. She did not have any parasitic infections.

The patient was born to consanguinous parents and had two brothers without any neuromuscular conditions.

3. Discussion

The first report on the association of idiopathic eosinophilic myositis with \( \text{CAPN}-3 \) mutations appeared in 2006 [6]. In this report the authors described their findings in six children and concluded that eosinophilic myositis may be the pre-dystrophic phase of LGMD 2A in at least a subset of patients with \( \text{CAPN}-3 \) mutations. Serum CK levels ranged between 4900 and 10377 IU/L. Eosinophil counts were reported in four patients, three of whom had mild or prominent hyper-eosinophilia. Two other patients with adult onset idiopathic eosinophilic myositis, who had been treated for this condition and also had a \( \text{CAPN}-3 \) mutation, were reported in 2008 [7]. Serum CK levels were given for only one patient and ranged from 5528 IU/L to 845 IU/L. There was no obvious correlation between the type and position of the \( \text{CAPN}-3 \) mutation and the occurrence of eosinophilic myositis in these reports [6,7].
The initial clinical picture with asymptomatic CK elevation suggested a muscular dystrophy rather than an inflammatory myopathy in our patient, even before the mutation analysis. However, the finding of prominent inflammatory infiltrates in the muscle biopsy and the marked fluctuations in the pre-treatment CK levels lead to the introduction of immunosuppressive therapy which was followed by a fall in the CK level which subsequently showed a reciprocal response to changes in the doses of the medications, especially of prednisolone (Fig. 1). Although the degree of weakness initially was quite mild, there was a subjective improvement in muscle strength and endurance after commencement of therapy. What was more striking however was the marked deterioration in lower limb strength and the spreading of the weakness to upper extremities which occurred over the 5-month-period when the immunosuppressive medications were tapered and discontinued. Given that all follow-up muscle examinations were performed by the same neurologist using the same manual muscle testing technique, the changes in muscle strength over this period cannot be attributed to inter-examiner variability. Although we cannot exclude the possibility that we were seeing the ordinary onset of clinical weakness due to the underlying dystrophic condition, the pace of the clinical progression was more rapid than would be expected and was more reminiscent of a subacutely evolving inflammatory myopathy, and suggested that the eosinophilic myositis may have accelerated the clinical course of the calpainopathy.

Although it has been put forward that eosinophilic infiltration might represent an early or transient developmental stage of calpainopathy [8], why and how this dystrophic process causes eosinophilic inflammation in some patients is enigmatic. It is not known if calpain-3 deficiency renders muscle tissue more susceptible to certain stimuli which induce eosinophilic inflammation, or if it has a role in modulating tissue eosinophil chemo-attractants. However, regardless of the mode of activation of the system, it is well appreciated that once the recruited eosinophils are activated they degranulate releasing several proteins into the target tissue [9] including eosinophil cationic protein (ECP), and major basic protein (MBP) which have been shown to induce muscle fibre membrane damage, which in turn causes fibre degeneration or necrosis [10,11]. The actions of MBP in eosinophilic myositis and in mdx mouse muscle suggest that it exerts its cytotoxicity through interaction with lipid membranes of the target tissues that eventuates in the loss of cytosolic proteins [11]. It has also been shown that ECP degrades both myofibrillar and cytoskeletal proteins leading to degeneration of muscle fibres [10].

Therefore, it is possible that in our patient the development of eosinophilic myositis caused further muscle injury with membranolytic destruction of muscle fibres and CK release. The recent finding that calpain-3 is a regulator of the dysferlin protein membrane repair complex [12] suggests that in the absence of calpain there may be a lack of effective repair of muscle membrane lesions induced by eosinophil products which might have an augmenting effect on the severity of the dystrophic process. It is not known if the origin of atopic dermatitis and infiltration in muscle are related in our patient. However, since the eosinophil counts and dermatitis symptoms paralleled the shifts in CK levels, it is possible that the immunosuppressive treatment directly affected this eosinophilic inflammation, as seen in other eosinophilic inflammatory conditions such as asthma. If this assumption is correct, it may mean that in the subgroup of patients with calpainopathy and eosinophilic myositis immunosuppression might slow the rate of progression of the disease, at least if introduced at an early stage. In contrast to many reported immunosuppressive responsive cases Pena Segura et al reported a 9-year-old patient with eosinophilic myositis of unknown aetiology who did not respond to corticosteroid treatment [13]. Corticotherapy was instituted after 2 years of untreated follow-up period in this case. Although it was not uttered in the report, if this patient had calpainopathy unresponsiveness might be due to the late introduction of immunosuppressive therapy.

Given that the CK and the eosinophil levels fell concurrently during therapy, the scenario that the corticosteroids act on eosinophil–muscle fibre interactions or on the effects of eosinophil proteins on muscle fibres would be possible. Alternatively corticosteroids and immunosuppressive agents could act on muscle fibre repair mechanisms. In vitro and in vivo studies are needed to test these hypotheses and to clarify this observation in our patient as it is important to judge the potential benefits of immunosuppressive treatment in at least a subgroup of patients with CAPN-3 mutations.

References