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Increased Frequency of Rhabdomyolysis in Familial Dysautonomia

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Abstract

Background—Familial dysautonomia (FD, OMIM# 223900) is an autosomal recessive disease featured by impaired pain and temperature perception and lack of functional muscle spindles. After 3 FD patients presented with rhabdomyolysis in a short time span, we aimed to determine the frequency of rhabdomyolysis is this population.

Methods and Results—In a retrospective chart review of 665 FD patients, 8 patients had at least 1 episode of rhabdomyolysis. Two patients had 2 episodes. The average incidence of rhabdomyolysis in FD was 7.5 per 10,000 person-years. By comparison, the average incidence with statins has been reported to be 0.44 per 10,000 person-years. Mean maximum creatine kinase (CK) level was 32,714 ± 64,749 U/l. Three patients had a hip magnetic resonance imaging showing gluteal hyperintensities.

Conclusions—Patients with FD have an increased incidence of rhabdomyolysis. We hypothesize that this may result from a combination of absent functional muscle spindles and muscle mitochondrial abnormalities.

Keywords

Autonomic disorders; Creatine kinase; Mitochondria; Skeletal muscle; Hereditary sensory autonomic neuropathy

INTRODUCTION

Familial dysautonomia (FD, Riley–Day syndrome, hereditary sensory and autonomic neuropathy type III, OMIM# 223900) is an autosomal recessive disease[1] due to mutations in the IkB kinase-associated protein gene (*IKBKAP*).[2] Mutations cause reductions of the protein product, IkB Kinase-associated protein/Elongator protein1 (IKAP/ELP-1)[3], which impairs development and maintenance of sensory and autonomic neurons. Skeletal muscle is also affected[4]. Hallmarks include impaired pain and temperature perception, afferent

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baroreflex failure, chronic lung disease, absent deep tendon reflexes, gait ataxia, and lack of functional muscle spindles, all of which contribute to morbidity and mortality[5].

Three of the FD patients we follow routinely in our clinic presented over a short time with episodes of rhabdomyolysis. We aimed to determine whether patients with FD have increased propensity toward developing rhabdomyolysis.

METHODS

We performed an Institutional Review Board-approved retrospective search using the New York University Dysautonomia Center database, an international registry of FD patients. The database has information on 669 FD patients worldwide, gathered longitudinally either during the visits (most FD patients come to our center for at least 1 annual evaluation) or from local doctors who send reports and/or test results. Rhabdomyolysis was defined as a creatine kinase (CK) level > 1,000 U/l[6]. We also studied the baseline CK value of 21 FD patients obtained during regular follow-up visits (i.e., outside rhabdomyolysis episodes).

An annual incidence rate was calculated according the formula d/y*10,000, where d is the number of rhabdomyolysis cases, and y is the number of people at risk (number of subjects * observation period).

RESULTS

Of the 665 registered patients, 8 had at least 1 episode of rhabdomyolysis. Two patients had 2 episodes. **Table 1** summarizes the patient characteristics. All were receiving fludrocortisone (dosages 0.05-0.2 mg/day) for orthostatic hypotension[7]. Except in 2 patients who had fever during the event, body temperature was normal. Mean age at event was 20.4 ± 6.3 years. Mean maximum CK level was 32,714 ± 64,749 U/l. Mean sodium during the episode was 140 mEq/L (range: 140-150 mEq/L); mean potassium was 4 mEq/L (range: 3.9-5 mEq/L). Myoglobinuria was not determined. Four patients (patients 1, 2, 3 and 5) had a hip magnetic resonance imaging showing hyperintensities, edema and/or fluid infiltration in gluteal muscles (**Supplementary Figure S1, available online**). The most common triggers were prolonged immobilization due to dysautonomic crisis or pneumonia in 4 patients, fever in 2 patients, and unknown in 2 patients. Except for 1 patient (who received at-home aggressive hydration), all were hospitalized and received intravenous fluids. All recovered without further complications.

Based on these results we calculated an annual incidence of rhabdomyolysis in FD of 7.5 per 10,000 person-years.

The mean baseline CK in 21 patients with FD (11 men, aged 23 ± 12.3) obtained during their regular follow-up visits was normal at 85.6±43.35 U/l (range: 22-159)[8]. One had a CK slightly below normal, but none had an elevated baseline CK level.

DISCUSSION

These findings show an increased incidence of rhabdomyolysis in patients with FD. The annual incidence rate of rhabdomyolysis in FD was 7.5 per 10,000 person-years. By comparison, the rate in patients on statins has been reported to be 0.44[9]. This emphasizes the apparent high risk for rhabdomyolysis in FD patients, despite normal baseline CK levels. It is conceivable that an FD patient may have had an undiagnosed episode of rhabdomyolysis or that patients or local doctors may have had failed to communicate a possible case. In this case, the frequency of rhabdomyolysis would be higher, thus emphasizing its relevance in FD.

None of the medications that patients were taking has been linked consistently to rhabdomyolysis. Interestingly, in 7 out of the 10 reported cases, muscle pain was a feature of rhabdomyolysis. Although patients with FD have impaired pain sensation, this indicates that deep muscle pain is preserved.

There are several possible causes for this predisposition to rhabdomyolysis. First, impaired pain sensation might have contributed to decreased mobility during prolonged recumbency. However, rhabdomyolysis has not been reported in other genetic neuropathies with sensory impairment, such as hereditary sensory autonomic neuropathy type IV (HSAN IV). In keeping with this, in a retrospective review of 64 patients with HSAN IV in our database, some of them recently reported[10], none had rhabdomyolysis.

Muscle spindles prevent over-stretching and muscle fiber damage[12]. Absence of functional muscle spindles in FD[11] may contribute to inadvertent muscle stretching during prolonged recumbency and lead to muscle damage.

Finally, it is also possible that FD patients may have a primary muscle dysfunction. Neuromuscular manifestations of FD have been poorly described. A case report found nemaline rods in the muscle biopsy of a patient with FD, possibly due to chronic denervation[13]. In this regard, we have reported that FD patients have a specific type of optic neuropathy similar to other hereditary mitochondrial optic neuropathies[14,15]. This raises the possibility that the mutation in FD affects mitochondrial protein synthesis either in the nervous system or other organs, such as skeletal muscle.

Mitochondrial function has not been studied thoroughly in FD. Cultured FD fibroblasts disclosed no mitochondrial dysfunction[16]. On the other hand, in a retrospective review of our database, we found a 14-year-old FD boy in whom activity of complex I, III, and IV mitochondrial enzymes in muscle were decreased, suggesting an electron transport chain disorder. Mitochondrial DNA analysis disclosed no mutations. Mitochondrial complex dysfunction has been associated with rhabdomyolysis[17], although this was not the case in this patient. Conditions such as dysautonomic crises, fever, and infections may also represent a more demanding metabolic state, which unmasks an underlying mitochondrial problem.

In conclusion, FD patients have increased incidence of rhabdomyolysis. Outside of these episodes, baseline CK is normal. We hypothesize that this may result from a combination of

absent functional muscle spindles and muscle abnormalities, perhaps related to mitochondrial dysfunction. Further studies are needed to confirm this.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

FD	Familial dysautonomia
CK	Creatine kinase
HSAN IV	Hereditary sensory and autonomic neuropathy type IV

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Table 1

Characteristic of patients with familial dysautonomia and rhabdomyolysis

Patient	Gender	Age at event	Medications at event	Symptoms	Maximum CK	Presumed trigger
1	M	23	Fludrocortisone Diazepam	Pain in left gluteal area	25,000	Prolonged immobilization during dysautonomic crisis
		25	Fludrocortisone Diazepam	Pain in left gluteal area	200,000	Prolonged immobilization during dysautonomic crisis
2	W	26	Fludrocortisone Diazepam Ranitidine	Pain in posterior thighs	49,655	Prolonged immobilization during dysautonomic crisis
3	W	20	Fludrocortisone Ranitidine Clonidine	Pain in right gluteal area	6,000	1-night polysomnographic study
		23	Fludrocortisone Ranitidine Clonidine	Swelling and pain in right gluteal area	6,500	Sleeping in a hotel with tight sheets
4	M	17	Fludrocortisone Ranitidine Clonidine Carbidopa	Swelling and pain over the left gluteal area	4,630	Unknown
5	W	30	Midodrine Fludrocortisone Clonidine	Pain in left gluteal area	1,290	Fever
6	M	18	Fludrocortisone	Pain in right thigh	3,508	Prolonged immobilization during pneumonia
7	M	16	Fludrocortisone Diazepam Clonidine Midodrine Pregabalin	Asymptomatic	2,696	Unknown
8	M	9	Fludrocortisone Midodrine Clonidine Carbidopa Gabapentin	Weakness and pain in posterolateral thighs	1,643	Fever due to viral infection

CK: Creatine kinase.