Unusual Presentations of Dystrophinopathies in Childhood

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X-linked recessive mutations in the dystrophin gene are one of the most common causes of inherited neuromuscular disorders in humans. Duchenne muscular dystrophy, the most common phenotype, and Becker muscular dystrophy are often recognizable by certain clinical features; however, less frequent presentations require a higher degree of suspicion. In this article, we describe a series of 6 children (4 boys, 2 girls) referred to a tertiary pediatric neuromuscular clinic for isolated elevated creatine kinase levels (range: 720–7000 IU/L) identified on initial assessment for otherwise unexplained transaminase elevations (n = 2), a social communication disorder (n = 3), and exertional myalgia and/or rhabdomyolysis (n = 1). There was no preceding family history of neuromuscular disease. One boy had an additional history of severe cerebral palsy and cyclical vomiting, and 1 girl had a history of maternal hepatitis C. There was no significant weakness at presentation, and the majority remained stable over a prolonged period of follow-up (age range at last follow-up: 9–16 years). All 6 children were found to carry dystrophin gene mutations resulting in milder phenotypes. This series highlights that dystrophinopathies may not uncommonly present with features distinct from the classic Duchenne muscular dystrophy and Becker muscular dystrophy phenotypes in both boys and girls. Pediatricians should be aware of such atypical presentations to initiate a timely and adequate diagnostic process. Establishing the correct genetic diagnosis of a dystrophinopathy is important to allow appropriate genetic counseling, to implement relevant surveillance and management strategies, and to avoid unnecessary investigations in search of an incorrect alternative diagnosis.

abstract

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X-linked recessive mutations in the dystrophin gene on chromosome Xp21 are one of the most common causes of inherited neuromuscular disorders. Duchenne muscular dystrophy (DMD), the most common phenotype, affects ~1 in 5000 males and typically presents with relentlessly progressive weakness from early childhood.[1,2] Although the typical presentation of DMD is fairly uniform and often recognizable by pediatricians, the Becker muscular dystrophy (BMD) phenotype is less common and more variable; it is associated with later onset and requires a higher degree of suspicion because weakness may be mild or still absent. Elevated serum creatine kinase (CK), or hyperCKemia, is the biochemical hallmark of the dystrophinopathies. DMD is usually caused by total deletion of the dystrophin gene due to out-of-frame mutations resulting in complete loss of functional dystrophin protein, whereas BMD is usually caused by in-frame mutations associated with higher quantities of residual dystrophin production.

In this article, we describe a series of 6 children who, after an incidental

TABLE 1 Presenting Features, Clinicopathologic and Genetic Data of Children With Atypical Dystrophinopathy Presentations

P	Sex	A	Presenting Feature(s)	CK (IU/L)	Other Clinical Features	Dystrophin Mutation	Prediction	Muscle Biopsy
1	F	12	Hypertransaminasemia (investigated for maternal hepatitis C)	1000–2000	Mild myalgia (from 6 y), toe walking	Deletion of exons 26–44 (in-frame)	BMD	Mild dystrophic changes
2	M	11	Social communication disorder	720–2000	Mild Achilles tightness, mild proximal weakness (MRC 4++)	Deletion of exons 31–44 (in-frame) (de novo)	BMD	Mild dystrophic changes, subtle dystrophin reduction on IHC
3	M	9	Hypertransaminasemia (investigated for cyclical vomiting)	2000–7000	Cerebral palsy, hyopituitarism	Deletion of exons 45–48 (in-frame) (maternally inherited)	BMD	ND
4	M	13	Social communication disorder	900–1150	Nil	c.1026C>T; p.Ala3421Val	BMD	ND
5	M	16	Myalgia and/or rhabdomyolysis	9000–5400	Toe walking, mild proximal weakness (MRC 4++)	Deletion of exons 10–29 (in-frame) (maternally inherited)	BMD	Mild dystrophic changes, subtle dystrophin reduction on IHC
6	F	11	Social communication disorder	2500–3400	Nil	Deletion of exon 56 (out-of-frame)	DMD	ND

The inheritance pattern of the dystrophin mutation has not been determined where not indicated. The prediction is the expected phenotype in boys. A, current age; IHC, immunohistochemistry; ND, not done; P, patient number.

discovery of hyperCKemia, were found to have a dystrophin mutation resulting in milder phenotypes (Table 1). Their presentations are discussed in detail, and we emphasize a combination of features that should raise the suspicion of a dystrophinopathy in patients who do not present within the classic phenotype. Family history of neuromuscular disease was not reported in any patient, and perinatal and developmental histories were noncontributory to the diagnosis.

PATIENT PRESENTATIONS

Patient 1

A girl was referred at the age of 4 years because of persistent hyperCKemia (1000–2000 IU/L) and elevated liver transaminases, detected incidentally on hepatology workup prompted by maternal hepatitis C. Developmental history was normal, although the patient's mother reported occasional falls. On examination, the patient toe walked, but there were no other signs of weakness or altered muscle bulk. At the age of 6 years, intermittent symptoms of myalgia emerged, but the results of the clinical examination remained unchanged. A muscle biopsy was performed and revealed mild dystrophic changes with normal immunohistochemistry. Dystrophin DNA analysis revealed an in-frame deletion of exons 26 to 44. Her further course remained stable, at the age of 12 years. Cardiac evaluations (ECG and echocardiogram) had unremarkable results.

Patient 2

A boy presented at the age of 3 years with toe walking, mild autism, and moderate hyperCKemia (>2000 IU/L). At presentation, he could walk and run easily but fell frequently. On examination, there was no muscle pseudohypertrophy or weakness, but mild Achilles tendon tightness was present. At the age of 4 years, he continued to toe walk and developed mild calf pseudohypertrophy but no muscle weakness. Repeat CK was mildly elevated (720 IU/L). The combination of pseudohypertrophy, toe walking, persisting hyperCKemia, and autism prompted dystrophin gene testing, which revealed an in-frame deletion of exons 31 to 44. He has remained functionally stable, with no complaints of myalgia or weakness, except a mild reduction of Medical Research Council (MRC) grades (4++/5) in neck flexion and shoulder extension. A period of clinical surveillance was elected over muscle biopsy because of the likely BMD phenotype. A cardiac evaluation revealed normal results at the age of 11 years.

Patient 3

A boy had a complex past medical history of quadriplegic cerebral palsy (Gross Motor Function Classification Scale Level V) due to hypoxic-ischemic encephalopathy. He was referred at the age of 5 years for persistent hyperCKemia (2000–7000 IU/L). Comorbidities included global developmental delay, autism, epilepsy, hydrocephalus, undescended testes, and hypopituitarism. HyperCKemia was first noted along with raised liver transaminases (aspartate transaminase >170 U/L) during frequent hospital admissions for recurrent unexplained cyclical vomiting, both prompting investigation for inborn errors of metabolism. Before neuromuscular referral, he maintained sitting balance, crawled fast, and mobilized with a Kaye walker, but in the preceding 2 years, his mobility declined to wheelchair use. On examination, he had bilateral cerebral palsy; muscle

power was not determined, but there was no pseudohypertrophy. In view of the persistent hyperCKemia (5748 IU/L), dystrophin gene testing was performed, revealing an in-frame deletion of exons 45 to 48. A muscle biopsy was considered to determine the degree of dystrophin reduction but was not pursued because of overall neurologic status and comorbidities. His further course has remained stable. His cardiac evaluation results were unremarkable.

Patient 4

A boy initially presented to his pediatrician with language delay and was subsequently diagnosed with intellectual disability and autism. Because of persistent hyperCKemia (907–1153 IU/L), he was referred to the neuromuscular service at the age of 10 years. A recessively inherited metabolic condition was initially suspected because of parental consanguinity. He had no symptoms of weakness, myalgia, or rhadomyolysis. Neuromuscular examination was normal. Dystrophin mutation analysis was performed. Deletion testing revealed negative results, but point mutation screening revealed a hemizygous variant (c.10262C>T; p.Ala3421Val) localizing to a region previously linked to intellectual disability.[3] A muscle biopsy was considered but was not pursued because of normal muscle power at age the age of 10 years, which was consistent with the prediction of a BMD phenotype. His further course has remained stable without evidence of weakness or cardiac involvement at the age of 13 years.

Patient 5

A boy was referred with myalgia and persistent hyperCKemia at the age of 6 years. Initial symptoms began shortly before the age of 2 years with progressive exercise-induced myalgia mainly affecting the hip girdle and quadriceps muscles. CK levels were elevated (9181–54 381 IU/L), and myalgia and urine discoloration suggestive of myoglobinuria and/or rhabdomyolysis was present. He did not have symptoms of muscle weakness, and developmental milestones were normal. Examination revealed a prominent muscle bulk of the quadriceps and deltoids but normal muscle power. A muscle biopsy (revealing mild dystrophic changes on light microscopy and a subtle reduction of dystrophin staining on immunohistochemistry) prompted dystrophin gene analysis, which revealed an in-frame deletion of exons 10 to 29. At follow-up age of 15 years, he continued to experience exercise-induced muscle cramps. Examination revealed a tendency to toe walk but no weakness. With advice, no further episodes of rhabdomyolysis and/or myoglobinuria occurred. Cardiac surveillance has revealed normal results, to date.

Patient 6

A girl was referred at the age of 9 years for isolated hyperCKemia (2555–3416 IU/L) incidentally detected on investigation for mild autism. Early motor development was normal. There was no suggestion of muscle weakness in the history or on clinical examination. Dystrophin analysis revealed an out-of-frame deletion of exon 56. A muscle biopsy was not performed because of a complete lack of weakness in this female carrier of a dystrophin mutation predicted to result in a DMD phenotype in boys. The family was counseled regarding the future risk for male offspring. Her cardiac evaluation results were unremarkable.

DISCUSSION

Although DMD is usually readily suggested by the combination of muscle weakness and raised hyperCKemia in boys in the first 5 years of life, some genetic alterations in the dystrophin gene may give rise to presentations that are not as instantly recognized and require a higher degree of diagnostic suspicion. With our series, we highlight several important observations that should alert the pediatrician to the possibility of a dystrophinopathy in both boys and girls with less severe or atypical presentations.

In patients with symptomatic hyperCKemia, patient history, clinical examination findings, and laboratory results often point to an underlying dystrophinopathy. However, CK levels do not always correlate with disease manifestations, which results in diagnostic difficulty, particularly in still asymptomatic patients[4] or, as illustrated in patients 1 and 6, in girls in whom an X-linked recessive condition is not immediately considered. Because hyperCKemia is almost always associated with the elevation of transaminases that are expressed in both the skeletal muscle and liver, hepatic pathology may be erroneously suspected, in particular if a history or additional symptoms thought to be suggestive of liver involvement are present, as illustrated in patients 1 and 3, respectively. To avoid unnecessary and invasive investigations, it is thus paramount to always include CK level determination in the assessment of patients with otherwise unexplained transaminase elevations.[5,6]

Although CK levels are typically much higher,[7] we also illustrate (patients 2 and 4) that CK levels <1000 IU/L should not preclude the consideration of a dystrophinopathy or the instigation of appropriate genetic testing.

Although boys with symptomatic DMD and BMD often experience myalgia and, less frequently, episodes of rhabdomyolysis, these symptoms in isolation (ie, without associated weakness)

have only rarely been reported in the dystrophinopathies.[8–11] The case of patient 5 (who presented with exertional myalgia and/or rhabdomyolysis and in whom a recessive metabolic myopathy was initially suspected because of parental consanguinity) reveals that a dystrophinopathy should always be considered in a boy presenting with such features, particularly if CK levels remain elevated at an interval. As illustrated by the same patient, whose mutation linked to a molecular region of the dystrophin gene previously associated with similar phenotypes,[11] evolution of associated weakness may be minimal, even over prolonged periods of follow-up. Additional central nervous system involvement reflective of brain dystrophin expression has been well-documented in boys with DMD and BMD[12] and comprises language, attention, and social communication difficulties. Patients 2, 4, and 6 in our series presented with social communication difficulties and hyperCKemia (on 1 occasion as low as 720 IU/L) but developed no or only minimal neuromuscular symptoms over a prolonged period of follow-up, suggesting that those features may indeed occur in isolation and be the sole presenting feature. Autism in a boy with hyperCKemia should thus always prompt dystrophin screening (even if CK levels are <1000 IU/L), but, as illustrated in patient 6, may also be a feature in manifesting female carriers.

Lastly, the case of patient 3 reveals that, corresponding to other common neuromuscular disorders, dystrophinopathies may also occur in the context of other neurologic conditions and that "double-trouble" ought to be considered in patients with unexpected progression or a coincidental finding of hyperCKemia.

CONCLUSIONS

Establishing the correct genetic diagnosis of a dystrophinopathy is important to allow appropriate genetic counseling, implement relevant surveillance and management strategies (including cardiac surveillance in female carriers), and avoid unnecessary investigations in search of an alternative diagnosis. In addition to the classic DMD and BMD phenotypes, dystrophinopathies may present with isolated hyperCKemia (occasionally <1000 IU/L) in the context of (1) other neurologic disorders, (2) exertional myalgia and/or rhabdomyolysis, (3) otherwise unexplained transaminase elevations, and/or (4) autism without associated weakness. Although the suspicion should be highest for boys presenting with such features, female carriers may occasionally manifest in early childhood. Pediatricians who are most likely to encounter these patients should be aware of such atypical presentation to initiate a timely and appropriate diagnostic process.

ABBREVIATIONS

BMD: Becker muscular dystrophy
CK: creatine kinase
DMD: Duchenne muscular dystrophy
MRC: Medical Research Council

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