The Diagnostic Difficulties of Complex Glycerol Kinase Deficiency

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Abstract
We describe 2 siblings with the contiguous X-linked gene deletion syndrome, complex glycerol kinase deficiency. The elder sibling demonstrated the difficulties diagnosing this rare condition. Affected children have the combined complications of congenital adrenal hypoplasia, Duchenne muscular dystrophy, and glycerol kinase deficiency. These patients illustrate the importance of genetic testing and prepregnancy counseling. In addition, they demonstrate the need for a multidisciplinary team approach in their management.

Keywords
glycerol kinase, Duchenne muscular dystrophy, adrenal hypoplasia

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Congenital adrenal hypoplasia is a rare condition typically presenting in the neonatal period. Affected patients are usually managed by experienced endocrinology services.1 The X-linked form resulting from the contiguous gene deletion syndrome is even more uncommon.1,2 Patients with complete deletions have glycerol kinase deficiency (GKD) and Duchenne muscular dystrophy (DMD) as well.1,3,4 As such, patients presenting with congenital adrenal hypoplasia should be screened for Duchenne muscular dystrophy and glycerol kinase deficiency. These patients require a multidisciplinary approach to their medical care. Failure to recognize patients with contiguous genetic syndromes results in delayed diagnoses and missed opportunities for genetic counseling.1,2 We describe 2 siblings, the elder of whom presented with atypical features of congenital adrenal hypoplasia leading to a delay in diagnosing that he also had Duchenne muscular dystrophy and glycerol kinase deficiency.

Case Histories

Patient 1

This boy was delivered at term in 1992, weighing 3.1 kg. His Apgar scores were 8 at 5 minutes and 10 at 10 minutes. His mother had 2 previous miscarriages at 6 and 8 weeks’ gestation; this was her first live-born baby, and the delivery was by caesarean section because of her obstetric history.

Following birth, he suffered transient tachypnea of the newborn, transient hypoglycemia, and he developed jaundice requiring phototherapy. His screen results for infections were negative. By day 19, he was dehydrated, jaundiced, had poor feeding, and intermittent vomiting. He was transferred to a tertiary center.

He was managed as if he were affected with congenital adrenal hyperplasia (CAH). However, because his 17-hydroxyprogesterone level was not significantly raised, this diagnosis was questioned from the start. He stabilized once commenced on hydrocortisone and fludrocortisone supplements.

A developmental assessment at 9 months of age confirmed global developmental delay. He had persistent hypotonia and a cognitive age of 4 to 5 months. These findings were thought to be related to a perinatal or postnatal insult having occurred. He was not dysmorphic. At 4 years of age, he had bilateral orchiopexies and a tonsillectomy. This patient remained wheelchair dependent. His global delay rendered him completely dependent for all his basic needs. At 5 years of age, his cognitive function remained at an 18-month-old level.

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At age 7 years, the incongruity of his lack of ambulation in association with calf hypertrophy and global weakness with absent reflexes was investigated. His serum creatine kinase level was raised (2507 mmol/L; normal range, 23-203 mmol/L). Absence of dystrophin on immunohistochemical staining of his muscle biopsy confirmed the diagnosis of Duchenne muscular dystrophy. Molecular genetic analysis confirmed complete deletions of all markers in the dystrophin gene region. He was noted to have mild hyperpigmentation dorsally over his proximal interphalangeal joints. These findings were in keeping with the diagnosis of congenital adrenal hypoplasia. Because congenital adrenal hypoplasia and Duchenne muscular dystrophy occur as part of a contiguous gene syndrome together with glycerol kinase deficiency, this patient was considered to have complex glycerol kinase deficiency.

His cardiac investigation findings remained normal until 13 years of age when reduction in his left ventricular ejection fraction was noted. He was not symptomatic, and the value improved after commencing an angiotensin-converting enzyme inhibitor.

As a neonate (day 19), he had metabolic acidosis (pH, 7.3; base deficit, −9 mmol/L; standard bicarbonate, 16 mmol/L). His serum sodium was 117 mmol/L, potassium was 8.5 mmol/L, urea was 13 mmol/L, and creatinine was 43 mmol/L. His blood glucose and thyroid function test results were normal. His 8:00 AM cortisol was 478 nmol/L (normal range, 28-662 nmol/L). His 17-hydroxyprogesterone level was 2507 mmol/L (normal range, 23-203 mmol/L). He had fewer intercurrent infections and improved after commencing an angiotensin-converting enzyme inhibitor agent. He remained stable on a low cholesterol diet.

On repeat investigations at 7 years of age, he had a persistently low 17-hydroxyprogesterone level of 0.6 mmol/L (normal range, <8 nmol/L), with a testosterone level of <1 nmol/L (0.5-2.7 nmol/L), dehydroepiandrosterone sulfate of <0.4 nmol/L (0.3-8 nmol/L), and random serum cortisol of 306 nmol/L (140-700 nmol/L). He had a normal fasting serum cholesterol and elevated fasting serum triglyceride level of 4.5 mmol/L (0.4-1.4 mmol/L). His elevated urinary glycerol concentration of 590 mmol/L reinforced the diagnosis of glycerol kinase deficiency. This abnormal lipid level was not considered in the range that would require medical intervention and was managed with dietary advice.

**Patient 2**

The younger sibling of patient 1 was delivered by elective caesarian section at term in 2000. The contiguous gene deletion syndrome affecting his brother was diagnosed while patient 2 was in utero. His mother received dexamethasone prior to delivery. At birth, the patient was noted to be hypotonic but required no resuscitation. His 17-hydroxyprogesterone levels were significantly reduced, and his serum creatine kinase was raised (5307 mmol/L; normal range, 23-203 mmol/L). He received hydrocortisone and fludrocortisone replacement therapy following birth. His course was not as complex as his older sibling. He had fewer intercurrent infections and improved motor development. He attained ambulation by 3 years of age and progressed with a more typical evolution of his motor abilities typical of boys with Duchenne muscular dystrophy in isolation. At age 7.5 years, he was walking with a waddling gait and having difficulty climbing stairs. His parents used a wheelchair for long distances. He attended a special school for children with moderate learning difficulties. His cardiac function remained normal, and he was managed with a prophylactic angiotensin-converting enzyme inhibitor agent. He remained on a low cholesterol diet.

Molecular genetic analysis confirmed that he also had a complete deletion of all markers in the dystrophin gene region. His serum cholesterol was normal with pseudohypertriglyceridemia. His urinary glycerol was elevated at 220 mmol/L, indicating glyceroluria.

**Discussion**

These children had complex symptomatology involving several specialized disciplines. The older brother eventually gained diagnostic confirmation of a contiguous gene deletion syndrome, and although his management was unlikely to be different, the genetic issues were of significance.

He was initially managed within an endocrine service, who managed his adrenocortical stability. Diagnostic debate continued from the outset in relation to the incongruities in his corticosteroid and initial 17-hydroxyprogesterone levels. His developmental delay was evident from infancy, but his initial neonatal hypoglycemia was not considered significant enough to be the cause for this. His developmental delay was thought to be the cause for his failure to gain ambulation. This compounded the deferred diagnosis of Duchenne muscular dystrophy. With hindsight, the clinical scenario seems clear, but in reality, most clinicians will concentrate on the problem at hand and the main concern relating to their specialization.

There is general consensus that boys with Duchenne muscular dystrophy have an increased risk of intellectual disability, most of which is within one standard deviation of the population mean, and approximately one third of whom have mean full-scale intelligence quotients below 70. The pathogenesis of intellectual disability remains unclear, but it is related to brain expression of dystrophin. Deletion of genetic material in the distal end of the gene is thought to be associated with an increased prevalence of learning disability. It is hypothesized that this area of the gene codes for specific brain isoforms of dystrophin, the absence of which results in an increased risk of intellectual disability. The intellectual disability is not thought to be progressive and does not correlate with the severity of the muscle disease.

Both our patients had deletions spanning the entire Duchenne muscular dystrophy gene confirmed on molecular genetic studies. The younger brother (patient 2) had oral steroid replacement therapy commenced immediately after birth. Steroid intervention is also a routinely recommended practice in the management of children with Duchenne muscular dystrophy, although there is no clarity about timing of treatment and exact dosage regimens.
The course of the younger sibling was far less complex than his older brother. Identification of the underlying cause from his first presentation enabled swift intervention. There is no doubt that he functions at a higher level than his brother, both cognitively and also in terms of motor capacity. The reasons for this remain unclear.

These patients had an extremely rare disorder; congenital adrenal hypoplasia alone is unusual with an estimated incidence of 1 in 12,500 live births.1,2 The combination with mental retardation and Duchenne muscular dystrophy represents a much smaller fraction of the hereditary group.2 The importance of diagnostic confirmation relates to early prognostic advice and genetic prenatal counseling.1,2

Most described cases of DAX1 deletions or mutations are published in the endocrine and genetic literature.1,3,4 Clinical details and management issues are rarely discussed in detail. These reviews also note the frequent early misdiagnosis of congenital adrenal hypoplasia as congenital adrenal hyperplasia, as occurred in our patients.1 Confusion arises as congenital adrenal hyperplasia is the most common cause of congenital adrenal insufficiency. Endocrine results from patients with congenital adrenal hypoplasia can be misleading.1

The condition has an inheritance pattern that is X-linked recessive and, as such, only manifests in males, which can lead to confusion with assumed virilization of a female with congenital adrenal hyperplasia until chromosomal analysis confirms XY status.3 This was initially the case in patient 1.

The association between congenital adrenal hypoplasia and hypogonadotropic hypogonadism is well documented.1,2,10,11 Unilateral/bilateral cryptorchidism is commonly associated with congenital adrenal hypoplasia, with a strong association between undescended testes and hypogonadotropic hypogonadism, with a strong association between undescended testes and hypogonadotropic hypogonadism: evidence that DAX-1 mutations lead to combined hypothalamic and pituitary defects in gonadotropin production. J Clin Invest. 1996;98:1055-1062.

Infantile glycerol kinase deficiency as part of the contiguous gene deletion syndrome is associated with increased levels of glycerol in blood and urine. Initially, infants present with pseudohypertriglyceridemia.11 Hyperglycerolemia is associated with hypoglycemia and osmotic dehydration.11

Most described patients with complex glycerol kinase deficiency present with salt wasting dehydration in the neonatal period. Psychomotor retardation is commonly described, but specific causes have not been clearly defined.11

Our patients highlighted the need for a multidisciplinary team approach and a central coordinating general pediatrician; the latter is often lacking in tertiary referral centers. While the initial medical management of an adrenogenital syndrome due to any cause is the same, making the exact diagnosis has definite implications in terms of genetic counseling and future pregnancies, as illustrated by these patients.1,2,4

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