Hydroxysteroid 17-Beta Dehydrogenase Type 10 Disease in Siblings

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Abstract Hydroxysteroid 17-beta dehydrogenase type 10 (HSD10) deficiency (HSD10 disease) is a rare X-linked neurodegenerative condition caused by abnormalities in the *HSD17B10* gene. A total of 10 mutations have been reported in the literature since 2000. Described phenotypes include a severe neonatal or progressive infantile form with hypotonia, choreoathetosis, seizures, cardiomyopathy, neurodegeneration, and death, as well as an attenuated form with variable regression. Here we present the second report of a c.194T>C (p.V65A) mutation in two half-brothers with a clinical phenotype characterized by neurodevelopmental delay, choreoathetosis, visual loss, cardiac findings, and behavioral abnormalities, with regressions now noted in the older sibling. Neither has experienced a metabolic crisis. Both of the siblings had normal tandem mass spectroscopy analysis of their newborn screening samples. The older brother's phenotype may be complicated by the presence of a 3q29 microduplication. Diagnosis requires a high index of suspicion, as the characteristic urine organic acid pattern may escape detection. The exact pathogenic mechanism of disease remains to be elucidated, but may involve the non-dehydrogenase functionalities of the HSD10 protein. Our report highlights clinical features of two patients with the less fulminant phenotype associated

with a V65A mutation, compares the reported phenotypes to date, and reviews recent findings regarding the potential pathophysiology of this condition.

Summary Sentence Hydroxysteroid 17-beta dehydrogenase type 10 (HSD10) disease (HSD10 disease) is a rare X-linked neurodegenerative condition with a variable clinical phenotype; diagnosis requires a high index of suspicion.

Introduction

Hydroxysteroid 17-beta dehydrogenase type 10 (HSD10) is a multifunctional NAD⁺-dependent mitochondrial enzyme involved in the degradation of isoleucine, metabolism of neuroactive steroids, and processing of mitochondrial tRNA transcripts (Yang et al. 2011; Zschocke 2012). It is encoded by the 3.11 kb *HSD17B10* gene, located on chromosome Xp11.2. The encoded protein, HSD10, is a 261 amino acid, 27 kDa protein which combines to form a 108 kDa homotetramer. It is the only 17-beta-hydroxysteroid dehydrogenase located in the mitochondria, and has a versatile active site that acts on a variety of substrates, including 17-beta-estradiol, allopregnanolone, isoleucine, fatty acids, bile acids, and xenobiotics (Holzmann et al. 2008; Yang et al. 2011).

HSD10 has been implicated in both childhood and adult-onset neurodegenerative conditions, such as HSD10 disease, MRXS10 disease, Alzheimer disease, and multiple sclerosis (Lenski et al. 2007; Yang et al. 2014). Missense mutations in the *HSD17B10* gene lead to HSD10 disease, a rare X-linked condition characterized by neurodegeneration, progressive visual impairment, choreoathetosis, and cardiomyopathy (Zschocke 2012). While primarily affecting males, variable X-inactivation has been described, leading to broad phenotypic expression in carrier females

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(Yang et al. 2013a). The first case of HSD10 disease was reported in 2000 by Zschocke et al. who described a 14-month-old boy with progressive cognitive and motor regression, choreoathetoid movements, loss of vision, and death at 3.5 years of age after developing intractable epilepsy (Ofman et al. 2003; Zschocke et al. 2000).

Disease pathogenicity was initially thought to be related to HSD10's function in isoleucine metabolism, as this enzyme is known to catalyze the 2-methyl-3-hydroxybutyryl-CoA dehydrogenation (MHBD) reaction in isoleucine metabolism. Those with HSD10 disease have elevated urine levels of 2-methyl-3-hydroxybutyrate and tiglylglycine, without increase in 2-methylacetoacetate as would be seen in beta-ketothiolase deficiency (Korman 2006). Unlike beta-ketothiolase deficiency, which is characterized by intermittent episodes of ketoacidosis often associated with illness, HSD10 disease follows a pattern of progressive neurodegeneration that is unresponsive to dietary or other intervention (Ofman et al. 2003; Yang et al. 2014). Pathogenicity is thought to be related either to an impaired role in metabolizing neuroactive steroids, such as 17-beta estradiol and allopregnanolone (Yang et al. 2007, 2009), and/or impaired processing of mitochondrial tRNA and mitochondrial dysfunction (Rauschenberger et al. 2010), as HSD10 is an essential component of mitochondrial ribonuclease (RNase) P (Holzmann et al. 2008).

Subsequent case reports identified another four patients with similar clinical features and metabolic profiles (Ensenauer et al. 2002; Sutton et al. 2003; Poll-The et al. 2004; Sass et al. 2004). Genetic analysis confirmed pathogenic missense mutations in the *HSD17B10* gene in these patients (Ofman et al. 2003). Over the past decade, a total of 10 missense mutations have been identified in about 20 cases of HSD10 disease (Yang et al. 2013b; Zschocke 2012). Whereas approximately 50% of these cases are associated with one common missense mutation, c.388C>T (p.R130C), other mutations have been reported as well. Less fulminant courses have been described, associated with the E249Q, L122V, Q165H, A145T, and V65A mutations (Olpin et al. 2002; Poll-The et al. 2004; Rauschenberger et al. 2010; Fukao et al. 2014; Seaver et al. 2011). In particular, the V65A mutation was reported by Seaver in 2011 in a case of a 10-year-old male with refractory epilepsy, choreoathetosis, ataxia, visual loss, and developmental regression with onset at approximately 2–3 years of life (Seaver et al. 2011). Here we present the second report of a V65A mutation in *HSD17B10* occurring in two half-brothers with neurodevelopmental delay, unusual movements, autistic features, and progressive visual loss.

Case History

A now 7-year-old male was referred at 19 months of age due to a family history of intellectual disability, visual impairment, and microduplication (dup 3q29). He was born at term without complications. Birthmother admitted to consuming alcohol during early pregnancy. Urine toxicology screen was negative. Hearing screen via otoacoustic emission was normal. Newborn screen by tandem mass spectroscopy (which included assessment for beta-ketothiolase deficiency and may detect deficiencies in 2-methyl-3-hydroxybutyryl-CoA dehydrogenase) was normal. He had two hospitalizations for bronchiolitis prior to the age of 7 months, the latter of which was complicated by *Klebsiella* urosepsis and probable endocarditis with Wolff-Parkinson-White (WPW) syndrome and mild left ventricular hypertrophy. After treatment with gentamicin, a hearing test identified sensorineural hearing loss. At 19 months of age he was noted to have delays in speech, fine motor, and social skills with some regression in social functioning. Chromosome microarray was normal, excluding the familial microdeletion, and Fragile X testing was normal. By 5 years of age he was having staring spells, had low truncal tone, and had been diagnosed with autism spectrum disorder with delays in speech, social skills, and toilet training. EEG revealed benign Rolandic epilepsy. Brain MRI was normal. Eye examination revealed pale optic nerves with foveal changes, suggestive of incomplete stationary night blindness. At about 7 years of age, he began to experience exertion-related spells of pallor, collapse, and near loss-of-consciousness felt to be related to WPW. Repeat echocardiogram showed increased left ventricular hyperplasia with mild diastolic dysfunction. In one of two urine organic acid analysis samples there was a characteristic pattern of elevated 2-methyl-3-hydroxybutyric acid and tiglylglycine without elevation of 2-methylacetoacetic acid, typical of HSD10 disease. A hemizygous c.194T>C (p.V65A) mutation in exon 3 of the *HSD17B10* gene was identified, confirming a diagnosis of HSD10 disease (Table 1). Given the lack of known treatment, and the clinical similarity to disorders of mitochondrial function (Rauschenberger et al. 2010), he was prescribed a “mitochondrial cocktail,” including coenzyme Q, Vitamins B1, B2, C, and E, acetylcysteine, and selenium, as well as digestive enzymes and probiotics. There has been subjective behavioral improvement noted by his family and teachers, but quantitative evidence for treatment effect has not been obtained. No further regressions have been observed.

Table 1 Reported pathogenic mutations in the *HSD17B10* gene

Patient	Genotype	Age of onset	Neurological findings	Developmental Findings	Regression (deceased)	Growth retardation	Visual loss	Hearing loss	Abnormal UOA	Reference
I-1 (F, adult)	c.194T>C (obligate), (p. V65A)	Unknown	Unknown	Learning difficulties in college	No	No	Unknown	Unknown	Unknown	N/A
II-1 (M, 7 years)	c.194T>C (p. V65A)	18 months	Hypotonia; benign Rolandic epilepsy; autism spectrum	Speech delay; behavioral issues	Progressive visual loss	No	Yes	Yes ^a	Yes	N/A
II-2 (M, 20 years)	c.194T>C, (p. V65A)	18 months	Decreased white matter volume of occipital lobes; cognitive impairment; choreoathetosis	Global developmental delays	Progressive visual loss	No	Yes	No	Yes	N/A
Number of reported cases										
One case	c.194T>C; p. V65A	2–3 years	Ataxia; choreoathetosis; dysarthria; seizures; hypotonia	Moderate cognitive and mild social impairments	Yes	No	Yes	Unknown	Yes	Seaver et al. (2011)
One case	c.745G>C; p. E249Q	6 years	Gait abnormality; dysarthria; hyperreflexia; dystonic posturing with upper extremity tremor; behavioral difficulties	Regression of verbal and motor skills	Yes	No	No	No	Yes	Olpin et al. (2002) (mutation info by Yang et al. (2009))
One Case	c.257A>G; p. D86G	Neonatal	Absent neurological development	N/A	No	No	Unknown	Unknown	Unknown	Rauschenberger et al. (2010)
One case	c.364C>G; p. L122V	Prior to 13 months	Broad-based gait; spastic paraparesis; increased lateral ventricle size; increased white matter perivascular spaces	Verbal and motor delays	No	No	Unknown	No	Yes	Poll-The et al. (2004) (mutation info: Ofman et al. (2003))
Ten cases	c.388C>T, p. R130C	Birth to 15 months	Motor regression; choreoathetosis; epilepsy; slight frontotemporal atrophy	Relatively normal development followed by progressive loss of milestones	Yes for males (death w/in several years of onset); no for females	No	Yes	No	Yes	Zschocke et al. (2000), Ensenauer et al. (2002) (mutation info: Ofman et al. (2003)), Sutton et al. (2003), Sass et al. (2004) (mutation info: Zschocke (2012)), Carzola et al. (2007), Garcia-Villoria et al. (2005, 2009), Zschocke (2012)

(continued)

Table 1 (continued)

Patient	Genotype	Age of onset	Neurological findings	Developmental Findings	Regression (deceased)	Growth retardation	Visual loss	Hearing loss	Abnormal UOA	Reference
One case	c.460G>A; p. A154T	6 years	Slightly below normal neurological development; normal MRI brain	Mildly delayed gross motor skills; difficulty with fine motor skills	No	No	No	No	Yes	Fukao et al. (2014)
One case	c.495A>C; p. Q165H	Not reported	Microcephaly	Growth retardation	No	Yes	Unknown	Unknown	Unknown	Rauschenberger et al. (2010)
Two cases	c.628C>T; p. P210S	3 months	Hypotonia	Developmental regression	Yes	No	Yes	Unknown	Unknown	Garcia-Villoria et al. (2009)
One case	c.677G>A; p. Q226R	1 day old	Myoclonus; seizures	Developmental regression	Yes (deceased at 7 months)	No	Unknown	Unknown	Unknown	Garcia-Villoria et al. (2009)
Three cases	c.740A>G; p. N247S	0–4 months	Ataxia, hyperkinetic behavior, myoclonus during stress	Psychomotor and speech delay	Yes for males (both deceased in infancy); no for female	No	Unknown	Yes	Yes	Garcia-Villoria et al. (2005), Chatfield et al. (2015)
Two cases	Silent mutation: c.574C>A; p.R192R (MRXS10)	1 month	Axial hypotonia; choreoathetosis; dysarthria; wide-based gait; lumbar lordosis	Motor delays	Unknown	No	No	Unknown	Unknown	Reyniers et al. (1999), Lenski et al. (2007)
Eight cases	Duplication Xp11.22	Unknown	hypotonic mouth; dysarthria; moderate intellectual disability; short attention span	Cognitive and speech delays	Unknown	No	Unknown	Unknown	Unknown	Froyen et al. (2008)

^a Noted after exposure to gentamicin

His older maternal half-brother, now 20 years old, had onset of global developmental delays, visual impairment, and behavioral disturbances with autistic features at a similar age as our proband. His history is also significant for cryptorchidism, left inguinal hernia, and mild dysmorphisms (coarse facial features, inverted nipples). His cognitive functioning is at the approximate level of a 2–3 year old. His visual difficulties were progressive and he is now legally blind. Full ophthalmological assessment is significant for myopia and progressive macular degeneration, with prolonged VEP responses consistent with optic nerve atrophy. He achieved walking at 2 years of age, but began to experience choreoathetoid movements during his childhood. These movements were more pronounced with ambulation and most prominent in his upper extremities, but also involved his face and lower extremities. With time, these movements have become nearly constant and are accompanied by intermittent dystonic posturing. By 19 years of age his gait had become slow, spastic, and shuffling with lower extremity hyperreflexia and sustained ankle clonus. More recently, he has experienced increasing difficulties with dystonia, thought due to a combination of side effects of psychiatric medication for aggression and his underlying HSD10 disease. An extensive work-up over the years, including plasma amino acids, urine amino acids, mitochondrial encephalopathy profile (including MELAS, MERRF, and NARP), 2-methylglutaconic acid, and testing for Leber Hereditary Optic Neuropathy were all normal. Free and total carnitine were mildly depressed. Chromosome microarray analysis identified a 3q29 microduplication, a finding known to be associated with mild to moderate cognitive impairment and mild dysmorphic features. EEG was normal. Brain MRI obtained at 8 years of age showed no structural abnormality, but decreased white matter volume of occipital lobes. Repeat MRI at 20 years of age showed progression of cerebral volume loss with increased ventricular size. Echocardiogram was normal at 17 years of age, but by 20 years of age showed decreased left ventricular size with moderate to severe concentric thickening. The characteristic HSD10 pattern was detectable on urine organic acid analysis; however, the findings were subtle and could have been consistent with recent ketosis. Analysis of the *HSD17B10* gene revealed the same hemizygous c.194T>C (p.V65A) mutation as seen in his younger half-brother.

The older brother's full sister shares his 3q29 microduplication, but not his *HSD17B10* gene mutation. She is a high school graduate with only mild cognitive disability. Their birthmother, a presumed carrier of the 3q29 microduplication and the HSD10 mutation, graduated from high school, but was diagnosed with learning problems and is reported to have "autism."

Discussion

HSD10 disease is a rare X-linked condition characterized by neurodevelopmental regression, choreoathetoid movements, hypotonia, progressive visual loss, hearing impairment, and seizures (Zschocke 2012). Despite few case reports (Table 1), a broad phenotypic spectrum has been described, ranging from a fatal neonatal form, to a rapidly progressive neurodegenerative infantile form, to an attenuated form lacking regression (Zschocke 2012). The severe R130C mutation accounts for approximately 50% of reported cases of HSD10 disease, possibly due to the presence of a hypermutable 5-methylcytosine prone to deamination (Yang et al. 2013b).

Here we describe the second case(s) of HSD10 disease associated with the V65A mutation first described by Seaver et al. (2011). The c.194T>C (p.V65A) mutation in *HSD17B10* results in the substitution in amino acid of an alanine for a valine in the HSD active site, which weakens interaction with NAD⁺. Our cases contribute important information regarding the V65A mutation phenotype, which is associated with a less fulminant clinical course than the more prevalent c.388C>T (p.R130C) mutation. Whereas R130C mutations generally result in severe neonatal or progressive infantile neurodegeneration with hypotonia, choreoathetosis, seizures, and death within a few years of onset, the V65A mutation causes a more prolonged course. The V65A phenotypes described here and by Seaver et al. (2011) share the features of abnormal choreoathetoid movements, dystonia, neurocognitive abnormalities, and progressive visual impairment, but lack the rapid deterioration described in individuals with the R130C mutation. Cardiomyopathy is a feature of the severe form of HSD10 disease (Zschocke 2012), and cardiac involvement, found in both of our patients, may be part of the expanded phenotype in attenuated cases. The neurodevelopmental regression in HSD10 disease appears variable, although regressions have become apparent in our older patient. Visual loss with myopia and bilateral optic nerve pallor is a common feature among all three V65A cases, as are social delays and abnormal choreoathetoid movements. The presence of hearing loss, autistic features and seizures are variably present (Table 1).

Interestingly, there appears to be a similar but distinct disorder, MRXS10 syndrome (OMIM #300220), caused by the silent c.574C>A (p.R192R) mutation. This mutation is associated with cognitive difficulties and choreoathetosis with normal vision. This abnormal HSD10 protein has essentially normal activity in catalyzing the MHBD reaction, but the amount of protein expression is reduced to approximately 60–70% (Lenski et al. 2007; Reyniers et al. 1999). Urine organic acid analysis was not reported.

Whereas HSD10 protein amount is reduced in MRXS10 syndrome, microduplication of the *HSD17B10* gene leads to higher protein levels and mild to moderate cognitive difficulties, dysarthria and shortened attention spans, without regression, choreoathetosis, or reported visual impairment (Froyen et al. 2008).

Researchers have tried to correlate clinical phenotype with residual HSD10 activity in the MHBD reaction of isoleucine metabolism, but the data appear variable and inconclusive (Yang et al. 2013b); R130C with 0–14% MHBD enzymatic residual activity, L122V with 25.4% residual activity, V65A with 50.5% residual activity, and R192R with 60–70% residual activity. Other mutations do not follow this trend: Rauschenberger describes a boy with a Q165H mutation and complete loss of MHBD enzymatic activity (<3% residual activity), who has normal neurologic development in the context of failure to thrive and microcephaly, and contrasts this with a case of a D86G mutation having 30% residual MHBD activity and a severe neonatal presentation that is fatal (Rauschenberger et al. 2010). Thus, impairment of the MHBD function does not appear to consistently correlate with the clinical phenotype of HSD10 disease.

Although a specific mechanism for the pathogenicity of HSD10 abnormalities remains elusive, researchers have been examining its function in mitochondrial ribonuclease (RNase) P (Deutschmann et al. 2014; Rauschenberger et al. 2010), and its role in the metabolism of neuroactive steroids (Yang et al. 2014). The *HSD17B10* gene encodes one of the three protein components of RNase P, an essential component of post-translational mitochondrial RNA processing (Holzmann et al. 2008). Variable disruption of mitochondrial morphology in cultured fibroblasts containing the Q165H, D86G, and R130C mutations has been demonstrated (Rauschenberger et al. 2010), with the amount of disruption being significantly higher in the more severe versus attenuated clinical phenotypes (Rauschenberger et al. 2010). A recent study of post-mortem tissue confirmed disrupted mitochondrial architecture and showed evidence of abnormal mitochondrial RNA processing, with markedly increased levels of unprocessed mitochondrial RNA in affected tissues (Chatfield et al. 2015). Such findings support the developing hypothesis that HSD10 disease is primarily related to an impairment of mitochondrial function.

The HSD10 protein also plays a vital role in the metabolism of neuroactive steroids, including allopregnanolone, an important modulator in gamma-aminobutyric acid type A (GABA_A) receptor functioning (Yang et al. 2009, 2014). Elevated levels of HSD10 negatively affect GABA_A receptor functionality. Interestingly, HSD10 amount is increased in Alzheimer disease, Down syndrome, and multiple sclerosis (Yang et al. 2014), all of which are associated with neurocognitive abnormalities.

The clinical characterization of our proband's older brother and their mother is complicated by the presence of a microduplication at chromosome 3q29 not present in the proband. The sister serves as a case control. 3q29 duplication syndrome is typically characterized by mild to moderate cognitive difficulties and microcephaly (Lisi et al. 2008). In the family presented here, the sister has the 3q29 microduplication and not the HSD10 mutation, and has minimal cognitive disabilities. Although we have considered the possible contribution of this microduplication in the older brother's neurocognitive disabilities, we believe that this is not the primary etiology underlying his significant global developmental delays, progressive visual disability, cardiac findings, abnormal neurologic exam and movements, and recently progressive course.

The diagnosis of HSD10 disease can be facilitated by urine organic acid analysis, which typically reveals elevated levels of intermediate metabolites of isoleucine metabolism (2-methyl-3-hydroxybutyrate and tiglylglycine). Unfortunately, the findings may be subtle, absent, or present only during times of metabolic stress. The pattern may mimic that of beta-ketothiolase deficiency (the next step in isoleucine metabolism), however, the absence of elevations in 2-methylacetoacetate excludes that diagnosis. Addition of an isoleucine load 6 h prior to measurement of urine organic acids can improve detection of HSD10 disease, particularly in carrier females, in whom diagnosis may require assessment of an additional metabolite, 2-ethylhydracrylic acid, to make the diagnosis (Garcia-Villoria et al. 2009). Acylcarnitine profile may also be abnormal, with possible elevations of C5:1 or C5-OH species (Fukao et al. 2014; Garcia-Villoria et al. 2005; Sass et al. 2004; Zschocke et al. 2000). Diagnosis is confirmed by identification of a disease-causing mutation in the *HSD17B10* gene. Though some states' newborn screening includes beta-ketothiolase deficiency in their panel of assessed conditions, it is important to note that tandem mass spectroscopy assessment of newborn screen samples in our patients was normal on initial and/or post-diagnosis reanalysis.

No standard or proven treatments options for HSD10 disease have been identified to date. As the disease pathogenesis appears independent of the enzyme's role in isoleucine metabolism, it is not surprising that dietary restriction does not ameliorate symptom progression (Ofman et al. 2003).

Conclusion

We present the second reported instance(s) of a c.194T>C (p.V65A) mutation in the *HSD17B10* gene causing HSD10 disease in two maternally related half-brothers. This

mutation is associated with an attenuated phenotype compared to the classic infantile form of HSD10 disease. Our report highlights the ophthalmologic, neurologic, cardiac, and behavioral aspects of this specific mutation as well as the subtleties of detection and diagnosis of this rare disease, which has characteristic but variably present metabolic features. Current newborn screening protocols are unlikely to detect this condition, and diagnosis requires a high index of suspicion. Pharmacologic or dietary interventions to reverse or slow the progressive nature of this complex multisystemic disease will require a better understanding of the enzymatic and cellular roles of this multifunctional protein.

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Compliance with Ethical Guidelines

Neither this work nor any similar work has been submitted for previous or simultaneous publication. The above authors have substantially contributed to the analysis of these cases and the writing or revision of the included manuscript and agree to its submission for publication.

Annelly Richardson – primary author, consolidated the case material for presentation, performed thorough literature review, wrote and edited the final manuscript for publication

Gerard T. Berry – provided metabolic genetics clinical consultation for these patients as well as expert analysis and critique of manuscript

Cheryl Garganta – provided expert analysis of clinical and laboratory data, and critique of the manuscript

Mary-Alice Abbott – primary geneticist of the patients described, initiated and supervised all aspects of the cases, data analysis, literature review, manuscript preparation, and final editing

Informed Consent

The patients and their guardians discussed provided their informed consent and permission to have their medical information discussed in this manuscript. Written documentation of verbal consent is available on request.

Conflict of Interest

Annelly Richardson, Gerard T. Berry, Cheryl Garganta, and Mary-Alice Abbott declare that they have no conflict of interest.

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