ONLINE FIRST

Banding Pattern on Polarized Hair Microscopic Examination and Unilateral Polymicrogyria in a Patient With Steroid Sulfatase Deficiency

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Background: Several forms of ichthyosis are associated with neurologic manifestations, including Sjögren-Larsson syndrome, Refsum disease, and mental retardation–enteropathy– deafness–neuropathy–ichthyosis–keratoderma (MEDNIK) syndrome. We report a case of X-linked steroid sulfatase deficiency, ichthyosis, seizures, abnormal hair banding pattern, and unilateral polymicrogyria.

Observations: A 3-year-old Caucasian male with a history of ichthyosis since birth presented with generalized tonic seizures. Findings from a physical examination were remarkable for thin hair, retinitis pigmentosa, and poor dentition. Polarized light microscopic examination of all the hair samples demonstrated a banding pattern. Magnetic resonance imaging of the brain revealed left hemispheric polymicrogyria with decreased sulcal pattern and stable asymmetric dilation of the left lateral ventricle. Constitutional microarray revealed the typical approximately 1.5-Mb deletion of the steroid sulfatase gene.

Conclusions: Steroid sulfatase deficiency is a cause of X-linked ichthyosis; however, our patient also had retinitis pigmentosa, seizures, and abnormal hair findings. The presence of abnormal hair with a banding pattern on polarized microscopy may be helpful for diagnosis; however, this pattern is not specific to this disease. In addition, to our knowledge, the presence of a malformation of cortical development has not been previously reported in patients with steroid sulfatase deficiency.

Steroid sulfatase (STS) deficiency is an X-linked ichthyosis condition, classically thought of as being primarily a dermatologic condition. A broader phenotype is beginning to emerge, and this disorder has been shown to increase the risk for attention-deficit/hyperactivity disorder, autism, and social communication deficits. The steroid sulfatase (STS) gene is located in chromosome Xp22.31 and codes for the STS enzyme, which is present in a ubiquitous distribution. Deficiency of placental sulfatase can lead to marked decrease in estrogens and dehydroepiandrosterone during the last weeks of pregnancy, leading to birth complications. After birth, this gene defect gives rise to X-linked ichthyosis. Approximately 10% of cases are part of a more complex contiguous deletion of the X chromosome, and the defect is associated with short stature, chondrodysplasia punctata, mental retardation, X-linked ichthyosis, Kallmann syndrome, and ocular albinism. The size of the deletion and the subsequent number of disrupted genes affect the final phenotype. Other conditions involving ichthyosis with prominent neurologic signs include Sjögren-Larsson syndrome, Refsum syndrome, and mental retardation–enteropathy–deafness–neuropathy–ichthyosis–keratoderma (MEDNIK) syndrome.

REPORT OF A CASE

HISTORY

The patient was born via cesarean delivery owing to fetal distress at 38 weeks with nuchal cord and meconium. He weighed 6 pounds and 2 ounces, was born with ich-
thyosis, and had an otherwise unremarkable hospital stay. Pyloric stenosis was diagnosed at 2 weeks, and the patient underwent a pyloromyotomy at the age of 3 weeks. Findings from computed tomographic (CT) scans and magnetic resonance imaging (MRI) performed at that time showed an enlarged left lateral ventricle, thought to likely be within normal variation. At 3 years and 3 months of age, he presented with a 1-year history of atypical absence seizures that usually lasted a few seconds, although some episodes lasted several minutes, and consisted of staring, eye fluttering, unresponsiveness, head drops, generalized limpness, and falling down. Once per week he had tonic seizures lasting about 2 minutes. In addition, he had pallid breath-holding spells occurring 3 times per week when he got upset, and these occasionally progressed into his usual tonic seizures, with the whole episode and seizure activity lasting about 2 minutes. The patient received levetiracetam, which seemed to increase his seizures.

FAMILY HISTORY

An older brother was noted to have ichthyosis and had had 1 febrile seizure. He was subsequently found to also have the STS deficiency due to Xp22.3 deletion. The patient’s mother had no abnormal skin findings and was healthy. She was found to be a carrier of the Xp22.3 deletion found in her sons. The remainder of the maternal family history was unremarkable. The patient’s father described difficulties in school. The paternal grandmother had neonatal losses in 2 pregnancies and a stillborn twin gestation. There was a history of autism in a paternal second cousin. The family was of French and mixed Caucasian descent. Consanguinity was denied.

PHYSICAL EXAMINATION

The patient was seen at age 3 years and 3 months. He had normal facies without notable dysmorphic features. He had very poor dentition, xerosis, with dry scaling on his flanks, bilateral shins, and shoulders. His hair was short and sparse. His head circumference was 49.3 cm, which was at the 50th percentile. The patient’s height was at the 20th percentile and weight at the 5th percentile. He had a tendency to flex his right wrist and had a tight heel cord in his right foot. A motor strength examination revealed a strength score of 4 on a scale of 0 to 5 on the right with increased tone. He did not have pincer function in the right hand and could grasp large objects for less than a minute. Examination of the deep tendon reflexes revealed 3+ on the right and 2+ on the left. Plantar responses were extensor on the right foot and flexor on the left. The patient revealed a wide-based gait with a right lower extremity weakness. Findings from an ophthalmologic examination demonstrated retinitis pigmentosa (RP) and no glistening white dots on the retina.

ANCILLARY TESTS

Full sequencing analysis of the ALDH3A2 gene was completed and did not show a mutation, thereby excluding Sjogren-Larsson syndrome from the differential diagnosis. Findings from additional studies included normal levels of plasma amino acids, acylcarnitine profile, and plasma carnitine, L-carnitine, ammonia, lactate, peroxisomal panel, and urine organic acids, and normal results from electrocardiography.

Chromosome analysis showed a normal male karyotype, which ruled out a large genomic rearrangement such as an X to Y translocation. Single-nucleotide polymorphism (SNP) microarray analysis was performed using the Affymetrix human genome-wide SNP 6.0 array (Santa Clara, California). The microarray revealed a genomic loss of approximately 1.6 Mb in size involving chromosome Xp22.31, with estimated genomic boundaries beginning at linear positions 6,477,902 and ending at 8,095,645 (National Center for Biotechnology Information Build 36, hg18) (Figure 1). This deletion was consistent with the known microdeletion syndrome, STS deficiency or X-linked ichthyosis (OMIM 308100). The KAL1 gene was not in the deleted interval.

Fluorescence in situ hybridization (FISH) analysis of metaphase and interphase cells was performed using a probe specific for the STS region, RP11-269D06. It showed signal patterns consistent with a deletion at chromosome Xp22.31, confirming the microarray findings. Subsequent FISH analysis of the maternal blood sample also showed deletion of RP11-269D06 at Xp22.31, indicating maternal inheritance of STS deficiency. The brother of the proband, also with abnormal skin findings, showed deletion of RP11-269D06. Four protein-encoding genes (HDHD1, STS, VCX, PNPLA4) and 1 microRNA gene (MIR651) were located within the common deletion. Of these, the only OMIM disease–associated gene was STS.

Electroencephalography (EEG) showed (1) intermittent runs of high-amplitude generalized spike and slow wave pattern with the lead in the left hemisphere; (2) bilateral spikes and slow waves, more prominent over the left hemisphere with increased synchronization during wakefulness; and (3) focal slowing in the left frontocentral region. During his seizures there was a diffuse spike and slow wave pattern in the EEG that was consistent with atypical absence seizures, which manifested as rhythmic eye blinking, behavioral arrest, and occasional head dropping during wakefulness. There was an overall decrease in the frequency of epileptiform activity following the introduction of clonazepam and lamotrigine.

Findings from an MRI scan of the brain demonstrated polymicrogyria throughout the left hemisphere, which was smaller in size with decreased sulcal pattern and stable asymmetric dilation of the left lateral ventricle (Figure 2). Despite the cortical abnormality and the decreased volume of white matter on the affected side, the white matter appeared normal. To further evaluate the integrity of the white matter, we determined the apparent diffusion coefficient (ADC) of white matter regions of interest on the diffusion-weighted imaging performed at ages 3 years and 3 months. The ADC values (reported in ×10−5 cm2/s) were similar to values described in the literature and ranged from 0.83 to 0.94.8,9 Region of interest analyses of white matter areas revealed no apparent diffusivity differences between the 2 hemispheres. The means (SDs) for the left hemisphere were 0.93 (0.04) and 0.93 (0.04) cm2/s.
frontal, parietal, temporal, and occipital, respectively, are as follows: 0.89 (0.04), 0.87 (0.06), 0.94 (0.06), and 0.83 (0.05); and for the right hemisphere: 0.86 (0.05), 0.93 (0.05), 0.93 (0.05), and 0.83 (0.06).

The patient’s hair was clipped for microscopic examination. The light microscopic examination showed normal cortical fibers (Figure 3A) with no evidence of trichorrhexis nodosa, trichoschisis, or ribboning. All the hair samples demonstrated a banding pattern under polarized light microscopy. The microscope stage was rotated on a horizontal plane; therefore, the hairs were rotated relative to the polarizing lens. The light and dark intervals were not regular and were reversible based on the rotation of the microscope stage, allowing the dark regions in the first position to become bright and vice versa on rotation (Figure 3B and C).

**FOLLOW-UP**

After the initial presentation to us at 3 years and 3 months of age, the patient continued to have atypical absence seizures twice daily and tonic seizures once a week. Further use of zonisamide failed to control his seizures. He is currently taking 50 mg of zonisamide twice a day and half a tablet of clonazepam twice a day (the tablet is 0.25 mg). The patient has dysarthria with delays in expressive language skills.

The patient described herein has a deletion at chromosome Xp22.31 that is consistent with STS deficiency. He has congenital ichthyosis, developmental delay, RP, atypical seizures, malformation of cortical development (MCD) with polymicrogyria and unilateral ventricular dilation, and a hair banding pattern that can be seen under polarized microscopy. In addition, he had pyloric stenosis soon after birth, which has been previously described in patients with STS deficiency. To our knowledge, this is the first case that associates MCD, seizures, and hair banding pattern with STS deficiency.

Lennox-Gastaut syndrome is composed of a triad of multiple seizure types (atonic, tonic, atypical absence, myoclonic, and generalized tonic-clonic), cognitive dysfunction, and slow spike-and-wave activity (slower than 2.5 Hz) on EEG. However, this syndrome is usually generalized and as a rule does not show lateralization of EEG activity. Our patient demonstrates a pseudo-Lennox-Gastaut syndrome with localization to the left hemisphere shown on EEG. The seizures possibly result from secondary generalization from the dysgenetic hemisphere. Unilateral hemispheric MCD, such as hemimegalencephaly, has been associated with epidermal nevus syndrome, hypomelanosis of Ito, Proteus

**COMMENT**

![Figure 1. Results of the microarray analysis showing a microdeletion of approximately 1.5 Mb at chromosome Xp22.31. The proximal breakpoint maps to 6,477,902 and the distal breakpoint to 8,095,645 (Build 36). Numbers on the vertical axis show the smooth signal, log2 ratio, and overall copy number state for all probes in the deleted interval (top to bottom). The position of the genes is represented along the bottom and shows that only 4 genes (HDHD1, STS, VCX, and PNPLA4) are included in the deleted interval.](attachment:figure1.png)
syndrome, and Klippel-Trenaunay-Weber syndrome. Findings from this patient’s dysmorphologic examination did not support a diagnosis of any of these syndromes.

To our knowledge, STS deficiency has not been previously recognized as a neurocutaneous syndrome, and our observation of the association of its skin and hair manifestations with polymicrogyria suggests that it may be. The finding that patients with STS deficiency are at higher risk for attention deficient disorder than the general population does further support the idea that this deletion could cause central nervous system dysfunction. However, pending further similar observations confirming or negating this association, we still need to acknowledge the possibility that the observed association in this patient may be coincidental.

The finding of RP in this patient is a novel clinical manifestation in someone with STS deficiency. X-linked RP is associated with multiple loci. There is 1 report of linkage of RP to Xp22, between markers DXS1223 and DXS7161. The interval between markers DXS1223 and DXS7161 (chromosome X: 8,353,912-18,864,466), is close to, but does not contain, the STS critical region. How a downstream deletion may affect development of RP in this patient is unclear but warrants further investigation.

The deletion interval that is common to both the unaffected carrier mother and brother with only the VCX3A gene, part of a family of genes containing 4 nearly identical paralogs on Xp22.3, has been proposed as the causative gene deleted in patients with X-linked nonspecific mental retardation. Several other studies, however, have shown that deletion of the VCX3A gene, as well as the other VCX paralogs in this region, are not sufficient to cause mental retardation. The SNP microarray analysis indicates that the region deleted in this individual, as well as his normally developing older brother, contains only the VCX gene and not the VCX3A or VCX2 genes. This finding gives further support to the idea that the VCX genes alone do not play a major role in cognitive development and/or that additional modifier loci are important in the development of mental retardation in individuals with STS deficiency.

A case report was made of a female patient with ichthyosis, epilepsy, mental retardation, hypergonadotropic hypogonadism, polyneuropathy, and cranial dysmorphisms. The patient was described as having Rud syn-

Figure 2. Magnetic resonance image of the brain in transverse view. A, Asymmetric dilation of the left lateral ventricle. RH indicates right hemisphere. B, Polymicrogyria throughout the left cerebral hemisphere.

Figure 3. Microscopic examination of hair. A, Cortical fibers within hair shaft (original magnification ×400). B and C, Hair under polarized light demonstrating a banding pattern (original magnification ×400). Arrows indicate a fixed position at 90° rotation and 180° rotation, respectively.
drome in the report. Rud syndrome is a term that has previously been used to classify a neurocutaneous disorder characterized by congenital ichthyosis, hypogonadism, and mental retardation. In most cases, epilepsy has also been present. In addition, there may be delayed growth or short stature. Retinitis pigmentosa, neurosensory deafness, and polyneuritis have also been described in these patients. Although STS may be deficient in some of these patients, normal STS activity has also been described in patients previously reported under the classification of Rud syndrome. Traupe suggested that the term Rud syndrome be abandoned owing to the different symptoms and genetic profiles of these patients. Alternatively, these syndromes should be reclassified according to the syndromes with better characterization.

This patient demonstrates a possible expanded clinical spectrum of STS deficiency that is the result of a deletion of the Xp22.3 locus with the presence of atypical seizures, MCD, unusual hair findings, and RP. What additional factors are contributing to his phenotype, which is different from others with STS deficiency, is unknown. It is possible that other genes modify the phenotype in a way that will modify the severity of ichthyosis in this syndrome. Many neurocutaneous syndromes, such as neurofibromatosis, have a highly variable clinical phenotype, even within families. To our knowledge, the presence of hair banding under polarized microscopy is a novel finding in STS deficiency. However, cysteine and methionine levels in the hair have not been measured, and concomitant trichothiodystrophy cannot be entirely excluded. Tiger-tail banding with polarized microscopy is classically described in the hair of patients with trichothiodystrophy, some of whom have a deficiency in cystine or methionine with affect sulfur content. However, banding may occur in other deficiency states, such as arginiosuccinic aciduria and acrodermatitis enteropathica. Banding has also been described in keratitis ichthyosis deafness syndrome and in pseudopili annulati. Although STS may be deficient in some of these patients, normal STS activity has also been described in patients previously reported under the classification of Rud syndrome. Traupe suggested that the term Rud syndrome be abandoned owing to the different symptoms and genetic profiles of these patients. Alternatively, these syndromes should be reclassified according to the syndromes with better characterization. 26

In summary, STS deficiency may have a more complex clinical phenotype than has previously been reported. It is possible that this may account for a portion of patients who were previously described as having Rud syndrome. Steroid sulfatase deficiency is seen in patients with X-linked ichthyosis; however, our patient also has RP, atypical seizures, MCD, and abnormal hair findings. The presence of abnormal hair with a banding pattern on polarized microscopy may be helpful in making a diagnosis; however, this pattern is not specific to this disease. To our knowledge, the presence of an MCD and hair-banding pattern has not been reported previously in patients with STS deficiency.

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REFERENCES

Mikhail Bulgakov: The Master and Syphilis

Immediately after Mikhail Afanasievich Bulgakov (1891-1940) finished his medical studies in 1916, he was ordered to run a rural hospital near Smolensk, Russia. His experience with more than 15,000 patients, seen within 1 year, is described in A Country Doctor’s Notebook.1 In the story “The Speckled Rash,” he masterly portrays his confrontation with syphilis. Prompted by intuition, he investigates the skin of a man who is about 40 years old:

[T]he light of the kerosene pressure-lamp shone on his yellow-tinted skin. A white, speckled rash showed through the yellow colouring of his flanks and bulging chest. “Like stars in the sky,” I thought to myself with a chill of fear. “This is it—syphilis,” I repeated grimly to myself. This was my first professional encounter with syphilis. Prompted by intuition, he investigates the skin of a man who is about 40 years old:

outpatient surgery records: “I had sat up the whole lonely night poring over the hospital records and the splendid German textbooks with their colourful illustrations.” In the records, he traces only cases of secondary and tertiary syphilis, not a single case of primary chancre. “[T]his means that the people here have no conception of syphilis and the lesions don’t frighten them. . . . I became convinced that syphilis was so fearful here precisely because it was not feared.” Finally, a young mother with 2 children, all 3 of whom were infected, motivates Bulgakov to set up an inpatient section for syphilitics, where he starts treatment with arsphenamine.

Bulgakov was born in Kiev, then part of the Russian Empire.2 As a soldier in World War II, he was wounded twice, which might explain his morphine addiction some years later. His interest in venereal diseases, at that time signifying almost exclusively syphilis, prompted him to practice as a venereologist in his home town of Kiev between 1918 and 1920. However, his statement “and I later devoted the best years of my life to venereal diseases”3 fits more his feelings than the facts. In the Stalin era, most of his stories and plays were considered counterrevolutionary and consequently forbidden, spoiling the last decade of his life.3 It was his widow, Jelena, fighting tirelessly for his rehabilitation, who succeeded in getting his finest work The Master and Margarita published, only 25 years after his death.

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