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SCA2 Presenting With Cognitive Regression in Childhood

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Abstract

Spinocerebellar ataxia type 2 (SCA2) typically presents in adulthood with progressive ataxia, dysarthria, tremor, and slow saccadic eye movements. Childhood onset SCA2 is rare and only the infantile onset form has been well-characterized clinically. This article describes a girl who met all developmental milestones until age 3 ½ years when she experienced cognitive regression that preceded motor regression by 6 months. A diagnosis of SCA2 was delayed until she presented to our emergency room at age 7 years. We document the results of her neuropsychological evaluation at both timepoints. This case broadens the spectrum of SCA2 presentation in childhood, highlights the importance of considering a spinocerebellar ataxia in a child who presents with cognitive regression only, and extends currently available clinical information to help clinicians discuss prognosis in childhood SCA2.

Keywords

Spinocerebellar ataxia

Introduction

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant disorder caused by the expansion of an unstable CAG repeat which encodes a polyglutamine tract in the *ATXN2* gene[1]. SCA2 typically presents in the fourth decade of life with slowly progressive cerebellar ataxia (truncal and limb ataxia), slow saccadic eye movements, dysarthric speech, tremor, and hypereflexia[2, 3]. The deep tendon reflexes are lost as the disease progresses, and peripheral neuropathy, ophthalmoparesis, and dementia are common[2, 4]. This report provides a detailed clinical description of a 7-year-old girl with SCA2 who presented to us with a 3 year history of developmental regression and progressive ataxia, however, her first symptom was cognitive regression that preceded motor regression by 6 months.

Case Report

This 7-year-old, right-hand dominant girl presented to the emergency center with a chief complaint of abnormal movements. She was a full-term infant born to unrelated parents of African American descent. She met all of her early language, cognitive, and motor developmental milestones. Her past medical history was significant only for hospitalization at age 3 years with a presumed viral illness associated with vomiting and dehydration from which

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she recovered well. At age 3 ½ years the family noted the onset of cognitive problems. A developmental evaluation from her school district documented a Developmental Quotient of 67 at age 3 years 7 months. Fine and gross motor skills appeared to be normal at that time.

After her fourth birthday, the patient's family noted problems with coordination, and she lost the ability to run. The motor problems progressed to the extent that she experienced falls, needed to hold on to the wall to walk, had trouble reaching for and picking up objects, and "shook so much" that she had a difficult time feeding herself. The family also reported further deterioration of expressive language, comprehension, memory, graphomotor skills, and behavior. She drooled at times and occasionally complained of pain in her eyes and legs. She was prescribed valproic acid at an outside institution for presumed epilepsy, but the medication was stopped by her mother after 3 months due to increased falls.

The family history was significant for a progressive gait disturbance in the paternal grandmother and the grandmother's sister with onset in their fifties. By report, the patient's father is in his twenties and is healthy.

Her general physical examination was unremarkable. The head circumference was 51.5 cm (60^{th} percentile). Her neurologic examination revealed a cooperative and alert girl who was oriented to person and place. Her speech was non-fluent, dysarthric, and not appropriately complex for age. Her cranial nerve exam was remarkable for bilaterally restricted lateral gaze with oculomotor apraxia. Her motor exam showed symmetric, full strength, normal muscle bulk, and mildly increased tone in her extremities. Her sensation was intact to light touch and pinprick throughout. The deep tendon reflexes were 2+ throughout but trace at the Achilles bilaterally. The left toe was upgoing. She had significant dysmetria on finger to nose and heel to shin tests as well as significant dysdiadochokinesis bilaterally. She had truncal ataxia, and she preferred to stand only with assistance. Her gait was wide-based and ataxic, and she walked on her insoles.

There were no retinal abnormalities on dilated ophthalmological exam. Nerve conduction studies demonstrated a sensory neuropathy with normal motor latencies, CMAP amplitudes, and conduction velocities. The EEG was significant for a diffusely slow background without evidence of an occipital dominant rhythm. There was diffuse cerebellar atrophy and mild cerebral atrophy on brain MRI. Laboratory evaluation included alphafetoprotein, IgE, IgA, vitamin E, ceruloplasmin, copper, lipid, lead, B12, homocysteine, methylmalonic acid, lactate, ammonia, plasma amino acid, and urine organic acid levels, transferrin isoelectric focusing, karyotype, chromosomal microarray, peripheral smear, and mitochondrial DNA studies; all were unremarkable. A panel to identify triplet repeat expansions in the most common ataxia genes revealed an expansion mutation of 72 CAG repeats in the SCA2 gene (*ATXN2*).

The results of neuropsychological assessment at age 7 years were consistent with diffuse brain involvement. During testing the patient was alert but highly distractible. She produced spontaneous speech but the content was often perseverative. Speech was slow and dysarthric but intelligible. Verbal utterances were short with a limited range of syntactic constructions. Comprehension was obviously impaired as well. Response times were slow to both verbal and nonverbal tasks. Fine motor control was too impaired to allow effective manipulation of a pencil. Intellectual functioning was assessed with the Stanford-Binet to be in the moderately to severely retarded range with a Full Scale IQ of 40, a Verbal IQ of 42 and a Nonverbal IQ of 43. The results of additional tests of receptive and expressive language were consistent with her overall level of intellectual functioning.

Discussion

The differential diagnosis for a child with cognitive and motor regression, progressive ataxia, dysarthria, and oculomotor apraxia is broad and includes neoplasm, mitochondrial disease, organic acidopathies, congenital disorders of glycosylation, and autosomal dominant or recessive cerebellar ataxias. Since the family history only hinted at possible autosomal dominant inheritance despite extensive questioning, our diagnostic evaluation was broad. Due to extensive clinical overlap among the spinocerebellar ataxias, most laboratories perform specific genetic testing batteries for the most common ataxias. This approach successfully led to the diagnosis of SCA2 in our patient.

Five neonatal or infantile-onset cases of SCA2 were reported in recent years with expansions between 62 and 500 CAG repeats. Four of these patients had between 230–500 repeats and presented with hypotonia, developmental delay, and a spectrum of pigmentary retinopathy, eye movement abnormalities, dysphagia, epilepsy, and early death[5, 6]. The patient with 62 repeats was described clinically at age 11 years, but he presented in infancy with eye movement abnormalities and developmental delay[7]. Two childhood-onset cases were identified in cohorts of patients with sporadic or dominantly-inherited ataxias. These patients had 64 and 57 CAG repeats and experienced the onset of neurological symptoms at age 6 years and 8 years respectively[8, 9]. Dirik et al. recently described an 8 year-old girl with normal early development who presented at the age of 5 years with ataxia, dysarthria, head titubation, and cognitive deficits[10]. At age 8 years she was bedridden due to ataxia, and had significant drooling, feeding problems, and bladder dysfunction. She was diagnosed with SCA2 due to 70 CAG repeats[10]. Interestingly, the degree of cerebellar atrophy is more pronounced in our patient with 72 CAG repeats, and she experienced the onset of symptoms more than a year before the child reported by Dirik *et al*. This is consistent with the inverse correlation between CAG repeat size and the age of onset of clinical symptoms; although the clinical course can vary between individuals and within kindreds[9]. The patient described above who presented in infancy with 62 repeats is an example of this clinical variation. In the Geschwind *et al*. SCA2 case series, repeat size accounted for 80% of the variability in age of onset[11]. Interestingly, they identified an African American kindred that was unique due to prominent dementia and rapid disease course. This kindred did have the largest average repeat size in their case series. Other adult case series estimate the prevalence of dementia in SCA2 as 34%[4, 12]. While genetic background, environmental influences, or somatic mosaicism may contribute to variability in the age of onset, rate of progression, and/or presence of dementia in SCA2, the patients described to date in the pediatric literature suggest that larger repeat size contributes significantly to these variables. The fact that all of the pediatric cases described to date share significant cognitive phenotypes ranging from developmental delay to cognitive regression (early dementia) supports the idea that larger repeat size is a significant contributor to the dementia phenotype. Our patient was able to ambulate with a weighted walker at hospital discharge, but within 6 months she required wheelchair assistance.

To our knowledge, this is only the second clinical description of a child with SCA2 and normal early development who subsequently developed cognitive regression, ataxia, and dysarthria in childhood. Our patient also had oculomotor apraxia. This is the first report to document cognitive status based on formal neuropsychological evaluation. Repeated assessment of cognitive abilities verified the family's report of developmental regression between the ages of 3 ½ and 7 years of age. By the age of 7 years, our patient's cognitive abilities were globally and severely impaired. This suggests that the diagnosis of SCA2 should be considered in children who experience cognitive regression as an isolated symptom since cognitive regression may precede motor symptoms. While an insistent family history should provide clues to direct the differential diagnosis, it is possible for a child to become symptomatic before other affected family members due to anticipation.

Early diagnosis will be very important as therapies to improve deficits or delay neurodegeneration are discovered. Watase *et al*. recently reported that lithium treatment improved motor coordination, learning, and memory deficits and partially restored the dendritic branching phenotype in hippocampal pyramidal neurons in a mouse model of SCA1[13]. Additionally, several groups demonstrated that histone deacetylase inhibitors improve neurodegeneration phenotypes in mouse models of Huntington's disease[14–16]. These recent advances provide hope that therapies to improve or delay triplet repeat disorder associated neurodegeneration will be available to patients in the next decade.

In summary, this case broadens the spectrum of SCA2 presentation in childhood, highlights the importance of considering a spinocerebellar ataxia in a child who presents with cognitive regression only, and extends currently available clinical information to help clinicians discuss prognosis with families of children affected by SCA2.

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