The patient presented to the psychiatric clinic for evaluation when he was in third grade due to behavioral and attention difficulties in school. He was unable to sit still, would not wait his turn, made inappropriate outbursts during class, and did not properly complete his work. He could not stay focused even in one-to-one conversation, and daydreamed frequently. Additionally, he often got into fights with his peers, leading to both school detentions and multiple suspensions. The mother reports that many of these symptoms had been present at a very early age.

Birth, medical, developmental, and family history were unremarkable. There was no history of anxiety, depression, psychosis, or suicide attempts, and no previous psychiatric hospitalizations.

The diagnosis of attention-deficit/hyperactivity disorder (ADHD) was made and he was started on medication treatment. He failed trials of both, amphetamines (Adderall XR, DuraMed) (up to 20 mg) and methylphenidate (Concerta, Janssen) (18 mg). On methylphenidate, he developed suicidal ideations and would get very irritable, stating, “kids were teasing [him] a lot.” He was started on dexamethasone hydrochloride (Focalin XR, Novartis), which was well tolerated. The dose was titrated up to 20 mg over a period of 8 months and an afternoon dose of dexamethasone hydrochloride 5 mg was added in response to residual afternoon symptoms of ADHD.

Two months later, the afternoon bridging dose was increased to 10 mg due to recurrence of declining grades, hyperactivity, and an inability to complete and turn in homework.

When the patient was 11 years old and in sixth grade, 1 month after his last adjustment in ADHD medications, he had an abrupt onset of neurological symptoms, including weakness in his lower extremities, gait instability, slurred speech, and confusion. He was hospitalized and his physical examination at that time was notable for photophobia, brisk deep tendon reflexes (DTRs), especially in the left side, left hand dysmetria, clonus in the left ankle, positive bilateral Babinsky, and unsteady gait.

His cerebrospinal fluid analysis (CSF) yielded mildly elevated CSF protein (59 mg/dL), negative meningo-encephalitis panel (Epstein-Barr virus, cytomegalovirus, herpes simplex virus 1 and 2, and human herpesvirus 6), and negative oligo-clonal bands. An MRI demonstrated symmetric posterior white matter changes with post-contrast enhancement, predominantly involving the periventricular and mesial temporal white matter, corpus callosum, posterior internal capsule, and adjacent cortico-spinal tracts with associated mild mass effect but no midline shift. MRI of the spine was mildly technically limited but showed no abnormalities. The patient was discharged home, but he returned to the hospital 1 month later with persistent headache, short-term memory loss and ataxia. An EEG was obtained and demonstrated episodic slowing without epileptiform discharges. An adrenocorticotropic hormone stimulation test identified adrenal insufficiency, so the patient was discharged home on hydrocortisone 8 mg/m2/day.

Editor’s note: Each month, this department features a discussion of an unusual diagnosis in genetics, radiology, or dermatology. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via e-mail at Pediatrics@Healio.com.
The results of his very long chain fatty acid profile were elevated (C26:0) and elevated ratios of C24/22 and C26/22, consistent with a diagnosis of adrenoleukodystrophy (ALD). For confirmation of his diagnosis, the ABCD1 gene mutation test was sent; which confirmed a positive novel frameshift mutation of the ABCD1 gene.

A month later, the patient had a seizure in school. The seizure semiology was unclear but it lasted less than 1 minute and was preceded by headache, vision changes, and emesis. The boy was prescribed levetiracetam (Keppra, UCB Pharma) 500 mg twice daily and has not had any recurrent seizures since then.

He continues having daily frontal headaches associated with photo-phobia, decreased vision, and at times seeing red and green “polka dots” that move across the visual field. They improve with ibuprofen and sleep.

His mother also notices diminished hearing and has to repeat herself loudly when speaking with him. He is forgetful and also at times hyperactive.

The boy continues taking dexmethylphenidate hydrochloride 20 mg even after getting diagnosis of ALD, since it seems to be effective for managing inattention, hyperactivity, and impulsivity, especially in the classroom setting. The psychiatrist also continues providing emotional support and care for this child and his family as they face a chronic and progressive condition with poor prognosis.

**DISCUSSION**

Deterioration in school performance can be a sign of multiple medical and psychiatric problems. The first case of ALD was described in 1910 by Haberfeld and Spieler; a previously healthy 6-year-old boy developed a deeply bronzed skin, impaired visual acuity, and deterioration in his school performance. The initial manifestations of ALD in childhood include signs of neurodegeneration with neurodevelopmental regression, adrenal insufficiency or both. Very frequently, symptoms and signs that are commonly used to describe psychiatric disorders are the initial manifestation of ALD; and the potential for initial misdiagnosis is significant.

Psychiatric symptoms may be the most prominent manifestation of this disorder for years, as occurred in our case: a boy who presented with symptoms of ADHD with only partial response to stimulants for 3 years, before developing any neurologic and endocrine symptoms that led to the diagnosis of ALD. Close to 70% of children who have ADHD have a positive response to stimulants such as methylphenidate. An additional 20% responds to the alternative class of stimulant medications. Poor response to these medications could possibly suggest the presence of a comorbid disorder.

ALD is an inherited metabolic storage disease associated with a defect in an enzyme that results in defective peroxisomal B-oxidation and the accumulation of very long chain fatty acids (VLCFA; C24, C26) in tissues of the body, especially the brain and the adrenal glands.

It results in demyelination associated with an intense inflammatory response in the white matter. ALD affects only boys.

Female carriers can manifest with some degree of disability. Approximately 70% of boys with ALD have adrenal insufficiency.

If no focality is found on the neurological exam, a brain MRI might be appropriately deferred, which would result in underdiagnosis of ALD. Elevated plasma VLCFA level is highly reliable in the diagnosis of ALD, which is confirmed by mutation analysis of the ABCD1 gene. Molecular studies are essential in determining a carrier state and especially in prenatal diagnosis, which can be performed in all peroxisomal disorders. MRI findings in ALD correlates with neuropathological features of bilaterally symmetric demyelination in the parieto-occipital region with involvement of the splenium of the corpus callosum. Although there is no definitive treatment, evidence suggests that early interventions before CNS involvement clinically and in MRI may offer a better prognosis to these patients.

Although a rare condition (the incidence of ALD has been estimated to be 1:17,000 newborns), ALD is very likely to present with symptoms and signs usually first brought to the attention of a child or general psychiatrist.

Clinicians must be mindful of the possibility of organic disease masking as a psychiatric disorder. It is very important to obtain a detailed medical and family history along with a thorough physical and neurological exam. When a patient is referred for developmental evaluation if school deterioration is a subject of concern, a test for adrenal reserves may be indicated.

**REFERENCES**