Late-Onset Adrenoleukodystrophy Associated With Long-Standing Psychiatric Symptoms

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Background: It is not commonly appreciated that patients with adrenoleukodystrophy (ALD) can first present in adulthood with psychiatric symptoms.

Method: This case study involved a 31-year-old man who was referred for a neuropsychiatric assessment of tardive dyskinesia and treatment-resistant psychosis. Upon neurologic examination, he was found to have spasticity, marked hyperreflexia with clonus, and bilateral Babinski signs. T_2-weighted magnetic resonance imaging demonstrated severe white matter disease. Metabolic screening revealed abnormalities of very long chain fatty acids consistent with the diagnosis of ALD. These results prompted us to review the literature on late-onset ALD with attention to (1) the nature of the associated psychiatric and neurologic symptoms, (2) the neuroimaging abnormalities associated with this disorder, and (3) treatment considerations.

Results: Individuals with adult-onset ALD may initially present with psychiatric symptomatology. Most commonly, these patients manifest signs of mania including disinhibition, impulsivity, increased spending, hypersexuality, loudness, and perseveration. ALD patients will often have upper motor neuron findings on neurologic examination. Despite the name of the disease, patients with ALD may not have clinical evidence of adrenal dysfunction. Neuroimaging reveals diffuse, confluent white matter lesions that typically originate in the parieto-occipital region. Both neuroleptic and anticholinergic medications may result in significant side effects with little resolution of the underlying psychiatric symptoms.

Conclusion: This case study and review of the literature illustrate the importance of performing neurologic and radiological examinations on all psychiatric patients with chronic illnesses. We emphasize the importance of reexamining and reimaging patients who are not responding to standard treatment. The clinical problem of "treatment resistance" should be seen as an indication that other diagnoses, such as an underlying metabolic disorder, need to be considered.

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Adrenoleukodystrophy (ALD) is an X-linked peroxisomal disorder that is associated with an abnormal accumulation of saturated, very long chain fatty acids (VLCFA). The disease process targets the white matter of the nervous system, the adrenal cortex, and the gonads, leading to central and peripheral demyelination as well as endocrine abnormalities.[1,2] Recently, the defective gene has been localized to chromosome Xq28 and found to code for a peroxisomal membrane protein that appears to hinder the ability of the enzyme VLCFA CoA-synthase to degrade VLCFA.[3,4]

The most commonly recognized form of ALD presents in boys between the ages of 4 and 8 years and begins with signs and symptoms of attention-deficit/hyperactivity disorder, followed by intellectual, behavioral, and neurologic deterioration. The illness progresses rapidly to a vegetative state within 2 years, with death soon thereafter.[5–8] Adult-onset ALD has been described and comprises at least 3 phenotypes: (1) adrenomyeloneuropathy (AMN), which predominantly affects the spinal cord, peripheral nervous system, and adrenal gland,[9] usually presents in the third decade of life with spastic gait, sensory impairment in the legs, and bladder dysfunction, suggesting a diagnosis of multiple sclerosis; patients with AMN often survive into the seventh decade[2,5,9]; (2) an AMN-cerebral form that may have all the features of AMN plus cerebral white matter involvement, which tends to be a more rapidly progressive illness; and (3) a pure cerebral form (< 2%), which is not associated with adrenal or spinal cord symptoms[2,8] and carries a very poor prognosis with an interval of only 3 to 4 years between the onset of neurologic symptoms and vegetative state or death.

The clinical focus in adult-onset ALD has been almost exclusively on the neurologic findings. Despite studies indicating that many of these patients will present with psychiatric syndromes, there is a relative paucity of detail re-

garding the nature of these psychiatric disturbances or their response to treatment.[10–18] We recently diagnosed ALD in a 31-year-old man who had been referred to us with tardive dyskinesia and a 10-year history of psychosis.

CASE HISTORY

Mr. A was the younger of 2 children with a sister 3 years his senior. His father left the family home shortly after Mr. A's birth and was never involved in his life. Although his birth and the majority of his early developmental milestones were normal, he did not speak until he was 4½ years old. His family described him as shy, withdrawn, and often inattentive. He was said to have "failed" kindergarten because of a "lack of interest," and following elementary school he attended vocational school until the age of 16 years. He then worked for a month as a manual laborer, but quit because of problems with his employer and has had no gainful employment since that time. While he had a history of substance use dating back to his midteens involving alcohol, cannabis, cocaine, amphetamines, and lysergic acid diethylamide (LSD), his family felt that his use was sporadic and "experimental" only.

He was first admitted to a psychiatry service at the age of 22 for assessment of his fitness to stand trial for a charge of theft after an attempt to steal musical records. He presented in a psychotic, manic state with euphoria, hypersexuality, and rapid, pressured, tangential speech. He endorsed both auditory and visual hallucinations as well as the delusional belief that he was an "undercover narc." His attention was good as measured by a task of serial subtractions, and his long- and short-term memory were intact. He was given a diagnosis of bipolar affective disorder complicated by substance abuse and was treated with haloperidol, 40 mg/day; nozinan, 50 mg at bedtime; and trihexyphenidyl, 6 mg/day. An electroencephalogram (EEG) showed no abnormalities. During the course of his 5-month stay, he recovered fully from his psychosis and was discharged home to live with his family.

Mr. A was readmitted to hospital 6 months later with suicidal ideation. His dog had recently died, and in an attempt to "join [his] dead dog," he tried to jump off of a bridge. At this time he was loud, rude, and disorganized with nonsensical, pressured speech. He was treated with lithium, 900 mg/day, as well as chlorpromazine, 400 mg/day. He was discharged after 9 days, but 2 days later he was readmitted to hospital with a similar manic presentation, this time after stealing lidocaine from the emergency room "to get high." He was again treated with lithium, 900 mg at bedtime, and discharged 1 month later. Neuropsychological testing revealed a full scale IQ of 70.

Less than a month later he was readmitted after unsuccessfully attempting to rob a bank while carrying a birthday cake. He had recently been abusing marijuana and cocaine and was clearly psychotic at the time. He was treated with fluphenazine decanoate, 25 mg i.m. twice a month, then discharged and lost to follow-up for several years. He was rehospitalized at age 28 and again at age 29, by which time he was noted to be grossly malnourished and physically ill with pneumonia. He was intrusive and distractible with delusions, hallucinations, disordered thinking, poor judgment, and a lack of insight. His orientation and recent and remote memory were intact, and no speech or gait disturbances were noted. He was treated with neuroleptic medication and transferred to a chronic care ward with a diagnosis of schizophrenia. It was revealed in this admission that he had had numerous offenses for violent and sexual assaults. These offenses were described in his file as "a function of his disorganized psychosis with a facile and hapless methodology, impulsively applied." Over the course of the next year he developed tardive dyskinesia, a gait disturbance, and significant swallowing problems that led to several episodes of aspiration pneumonia. There was no improvement in his psychosis during this time despite numerous changes in his antipsychotic regimen. Cranial radiological investigations were never carried out.

Neuropsychiatric Presentation at the Time of Admission

Mr. A was referred to McMaster University Medical Centre, Hamilton, Ontario, Canada, for assessment and treatment recommendations regarding his tardive dyskinesia and poor response to antipsychotic medications. As noted above, he carried a diagnosis of schizophrenia, and at the time of the assessment he had been continuously hospitalized for 2 years. Apart from recurrent episodes of aspiration pneumonia, his medical history was entirely negative. Little of his family history was known except that he had a paternal uncle who had been admitted to a psychiatric ward. Current medications included loxapine, 25 mg at bedtime; trihexyphenidyl, 5 mg t.i.d.; and omeprazole, 20 mg o.d.

He presented to us as a very thin, wide-eyed, frightened-looking young man whose mouth hung open and who was drooling. His eyes darted around the room, and his paranoid fear of being harmed prevented us from performing full neurologic and psychiatric examinations. His speech was difficult to understand, and he displayed facial grimacing. Dyskinetic movements of his mouth, tongue, and trunk were apparent, and he had prominent tongue thrusting. His gait was wide-based, unsteady, and appeared spastic. He held his left arm extended alongside his body with no arm swing, and he positioned his right arm across his chest, holding onto his left arm. It was difficult to determine if he was hallucinating.

The patient was brought into hospital for a period of observation. His vital signs were normal. He was fully alert, but disoriented to place, time, and date. His attention was poor, and he required frequent redirection. His

immediate and short-term memory were intact. He was restless, impulsive, and disinhibited, repeatedly stating "I love you" and attempting to touch those around him in an inappropriate sexual manner. At times he was incontinent of urine. He eventually allowed a full neurologic examination that revealed the following: cogwheel rigidity in all limbs; hyperreflexia, greater on the left than the right; sustained ankle clonus bilaterally; bilateral Babinski responses; primitive reflexes; and a negative Romberg test. Assessment of his speech revealed moderately severe spastic dysarthria. All aspects of his examination were characterized by distractibility, disinhibition, and stimulus boundedness. For example, during finger-nose testing he would bring his nose to the examiner's finger or try to grab or kiss the finger that was held out to him. Problem solving and abstract reasoning were markedly impaired, and his responses were often inaccurate and vague. He was able to follow commands, but frequently perseverated and was unable to successfully complete most tasks.

Investigations

Initial laboratory investigations included urinalysis, complete blood counts, serum electrolytes, urea nitrogen, creatinine, calcium, phosphorous, cortisol, vitamin B_{12}, and folate levels, as well as venereal disease research laboratories (VDRL), assessment of his human immunodeficiency virus status, thyroid indices, and liver functions. All of these tests were normal except for his vitamin B_{12} level, which was elevated at 761 and 1107 pmol/L on 2 separate occasions (normal range, 133–500 pmol/L). EEG studies showed no abnormalities. Assessment of Mr. A's swallowing ability confirmed moderate, oropharyngeal dysphagia. Given the clinical constellation of (1) cognitive deterioration, (2) treatment-resistant psychosis, and (3) an abnormal neurologic examination including significant upper motor neuron findings, further investigations were ordered. Magnetic resonance imaging (MRI) revealed marked white matter disease involving predominantly the left and right centrum semiovale, corona radiata, and parietal regions (Figure 1). In addition, there were pinpoint areas of abnormally high signal intensity in the basal ganglia and pons bilaterally. Electromyography (EMG) studies showed evidence of slowed impulse conduction in both sensory and motor nerve fibers with mild axonal loss among the sensory nerve fibers of the hand. Sural nerve biopsy revealed changes consistent with a chronic inflammatory neuropathy.

Given the MRI and EMG results, we initiated an investigation for dysmyelinating disorders known to occur in association with psychiatric disturbances. Vitamin B_{12} levels were high and serum homocysteine level was within normal limits, ruling out cobalamin deficiency. Serum levels of arylsulfatase (for metachromatic leukodystrophy) and β-galactosidase (for Krabbe disease) were likewise within normal range. His VLCFA were elevated as follows: $C_{26:0}$ was 2.796 nmol/mL (normal range = 0.83 ± 0.46 nmol/mL), and the ratios of $C_{24:0}/C_{22:0}$ and $C_{26:0}/C_{22:0}$ were 1.10 nmol/mL and 0.070 nmol/mL, respectively (normal ranges: $C_{24:0}/C_{22:0}$ = 0.84 ± 0.08 nmol/mL and $C_{26:0}/C_{22}$ = 0.013 ± 0.009 nmol/mL), consistent with a diagnosis of ALD. A discriminant function incorporating all 3 measuresments has been developed that provides complete separation of controls from ALD cases.[19] Applying this function to our patient gave a value of 13.46, placing him clearly outside the normal range. His serum testosterone level was normal at 18 nmol/L. Serum follicle-stimulating hormone and luteinizing hormone (LHS) levels were normal at 4.9 IU/L and 6.8 IU/L, respectively. His 10-a.m. cortisol level was normal at 560 nmol/L (normal range, 200–600 nmol/L). A corticotropin level at this time was 153 pmol/L (normal range, 4–22 pmol/L) and a corticotropin-stimulation test was outside normal limits with his baseline cortisol of 220 nmol/L dropping to 214 nmol/L 1 hour later, indicating a need for replacement therapy.

DISCUSSION

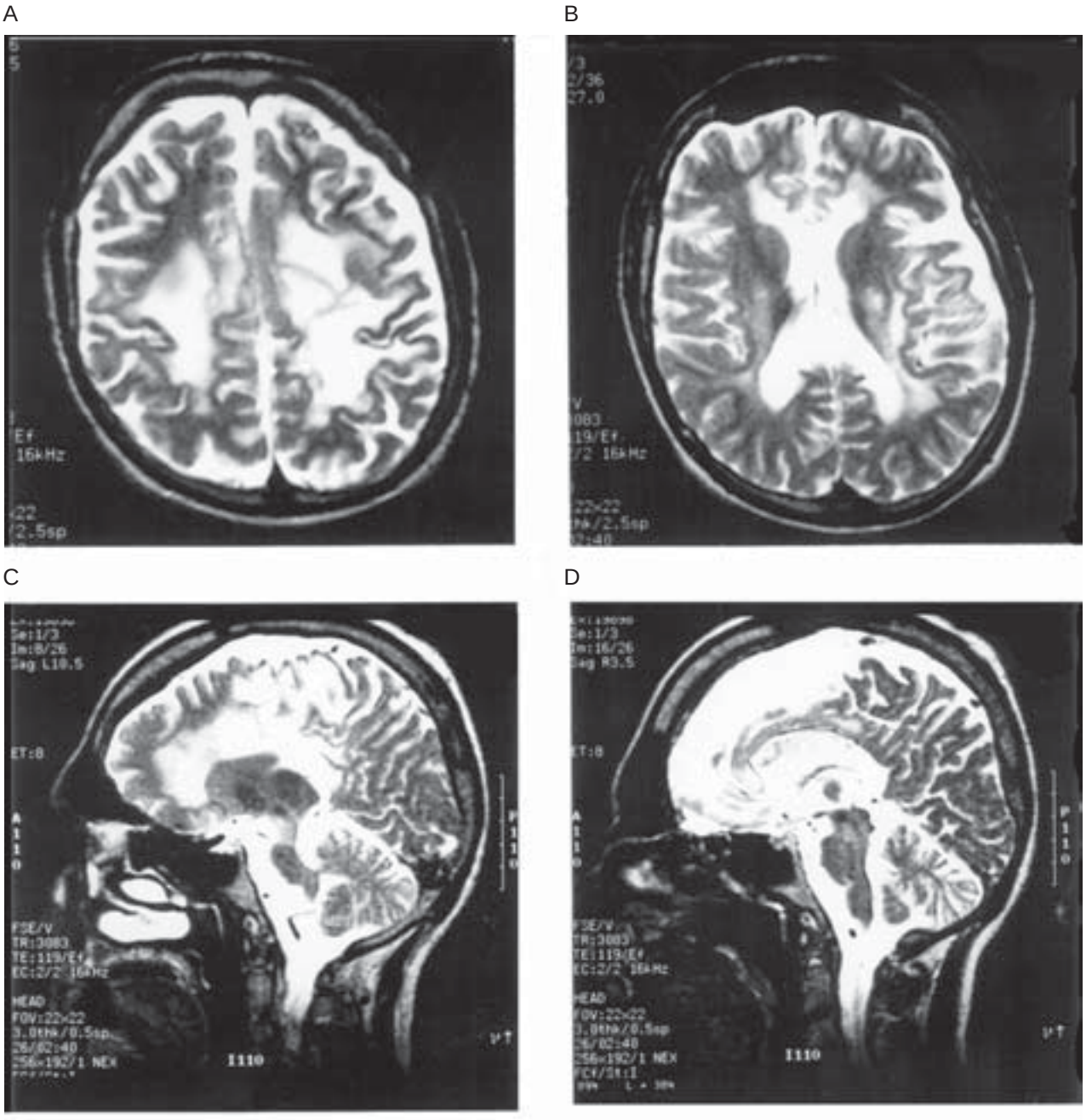
This 31-year-old man with a history of multiple psychiatric diagnoses was found, after almost 10 years of psychiatric treatment, to have adrenoleukodystrophy, most likely AMN-cerebral subtype. The diagnosis was made during an assessment for what was thought to be simply tardive dyskinesia and a 2-year period of "treatment-resistant psychosis." This case illustrates several underappreciated aspects of ALD: (1) there is an adult-onset form of the disorder, (2) at least 30% of patients with adult-onset ALD do not have abnormal baseline cortisol levels, and (3) ALD may present initially with psychiatric disturbances. The clinical emphasis has, for the most part, focused on the early-onset forms of ALD, and even in these the psychiatric manifestations have been largely ignored. Indeed, in most major psychiatric textbooks[20,21] ALD is not included as a disorder that may cause or present as psychiatric illness, an omission which may lead to underdiagnosis in psychiatric populations.

Clinical Features of ALD

Psychiatric features. There is very little information in the literature regarding the incidence of psychiatric symptomatology in patients with ALD, although one study suggests that it may be quite high.[10] Kitchen et al.[10] reviewed 109 cases of ALD, 6 of which presented after the age of 20. Of these 6, 4 had psychiatric symptoms at the time of presentation, and 1 of the 4 had only psychiatric symptoms. Unfortunately, this and most other published reports provide few specific details regarding the mental status of these patients.

We could find only 12 cases in the English literature that provided detailed information about the nature of the

Figure 1. Magnetic Resonance Imaging (MRI) T_2-Weighted Coronal (A, B) and Sagittal (C, D) Images Showing Extensive Confluent White Matter Lesions, Predominantly Bilateral, With Prominent Cortical Atrophy



psychiatric disturbances in patients with adult-onset ALD.[11–18] These are summarized, along with our case for comparison, in Table 1. It is noteworthy that 10 of the 13 cases presented with psychiatric symptoms as their initial manifestation of the disease. Twelve patients had symptoms of mania including disinhibition, emotional lability, increased spending, hypersexuality, loudness, and perseveration; 5 of these patients were also psychotic. In 9 of the 13 cases, patients developed dementia within 1 to 2 years after the onset of neurologic symptoms. Seven of the 13 had no evidence of adrenal insufficiency at the time of presentation, although 4 of the 7 went on to develop adrenal dysfunction later in the course of the disease.

Neurologic features. We were able to find only 37 cases, including the 13 outlined in Table 1, that provide a detailed description of the neurologic manifestations of

adult-onset ALD.[11–18,22–38] In 34 (92%) of the 37 cases, there was clear evidence of upper motor neuron findings, including hyperreflexia and extensor plantar responses; these produced disturbances ranging from abnormal gait (usually spastic or ataxic) (31/37) to urinary incontinence (18/37). In all cases, the lower extremities were preferentially targeted with the upper extremities relatively spared. Twenty-three patients (62%) had evidence of sensory neuropathy, 9 (24%) were reported to have visual field defects, 10 (27%) had dysarthria, and at least 6 (16%) developed aphasia.

A large proportion of the well-described cases of adult-onset ALD were characterized by cognitive decline. Only one case in the literature other than ours made note of developmental delay preceding cognitive decline.[12] Another patient who had a low IQ when first tested had previously completed his studies for dentistry.[17] We assume this represents cognitive decline and not a long-standing problem. Ten of the 13 patients described in Table 1 showed clear evidence of cognitive impairment, and in most cases for which longitudinal observations were available, there was evidence of cognitive decline.

Endocrine abnormalities. The adrenal dysfunction in ALD targets the cortex, with relative sparing of the medulla. ALD has been shown to be one of the most frequent causes of Addison disease in men, and adrenal insufficiency may be the only clinical expression of ALD in 8% of those with the disease.[39] While adrenal insufficiency precedes the onset of neurologic dysfunction in 50% to 60% of adult-onset cases, one third of cases will have normal adrenal function at the time of presentation.[2,40] Plasma corticotropin level is considered to be a sensitive marker for adrenocortical dysfunction in patients with ALD.[40,41]

Adult-onset ALD is associated with testicular dysfunction in up to 80% of patients.[42] Testosterone levels are usually normal, although the testosterone/LH ratio is significantly lower than in controls in 82%, reflecting damage to the Leydig cells. Fifty-four percent of patients with ALD will have varying degrees of sexual dysfunction, most commonly impotence.[42]

Neuroimaging Abnormalities Associated With ALD

In a study[5] of 76 men with neurologic findings compatible with AMN, abnormal brain MRI studies were found in 46%. These individuals constitute the so-called AMN-cerebral subgroup. Ninety-three percent of those with abnormal MRIs had involvement of the white matter in the temporal region, and 61% had involvement of the parieto-occipital region. Other affected areas (in decreasing order of severity) included corpus callosum (40%), frontal regions (24%), and cerebellum (24%). There were other, less characteristic patterns, however, such as early frontal lobe involvement (seen in approximately 15% of patients) or an asymmetric mass lesion often mistaken for brain tumor.[43–47]

In addition, the visual and auditory pathways were abnormal in 77% and 63% of patients, respectively. Interestingly, in spite of the frequent MRI abnormalities in the visual pathways, visual evoked potentials were abnormal in less than 5% of patients.[5] This is an important point of distinction from multiple sclerosis, since the majority of patients with multiple sclerosis have visual evoked potentials outside normal range. Brain stem auditory evoked potentials were outside normal limits in more than 90% of ALD patients.[6]

All patients for whom there are detailed psychiatric data had abnormal MRI scans (10/13) (see Table 1). The majority (7/10) had large confluent white matter lesions in the temporal and occipital horns, with 3 of these cases having more extensive demyelination involving the frontal and parietal areas. The remaining 3 patients had periventricular T_2-weighted hyperintensities. In 3 of 4 cases in which a cranial computed tomography (CT) was also obtained, the imaging was virtually normal (at a time when the MRI was grossly abnormal), demonstrating that the CT is an insufficient screen for white matter disease.

Diagnostic Considerations

Family history. Since ALD is an inherited disorder, a careful family history is an important component of the diagnostic assessment. One has to inquire about a range of disturbances given the striking phenotypic variability in the way ALD can present within a given family.[22,34,41,48] Of particular relevance is a family history of adrenal insufficiency (Addison disease), progressive gait disturbance, urinary incontinence, mania, or early infant deaths in male children. Another diagnosis worthy of specific inquiry is that of multiple sclerosis, since 20% of women heterozygous for the ALD gene have neurologic symptoms and are often given this diagnosis.[2,49] Unfortunately, it is often difficult to obtain an accurate or complete family history, if, as often happens with ALD, the patient is psychotic or cognitively impaired.

Clinical awareness. There is a strong possibility that many cases of ALD among psychiatric patients may go unrecognized. Several factors may contribute to this. For instance, it is not commonly appreciated that inherited metabolic disorders can present for the first time in adulthood. In the case of ALD, for example, we found very few references to this disorder in the adult psychiatric literature. This unawareness results in a low index of suspicion and failure to order the appropriate diagnostic tests. Compounding the problem is the fact that many psychiatry patients do not receive a thorough neurologic examination or cranial MRI scanning, either of which may reveal evidence of white matter pathology that merits further investigation. When neurologic abnormalities do become apparent, these may be erroneously ascribed to neuroleptic medication. This was the case with our patient, whose spasticity was misinterpreted as parkinsonian rigidity and attributed to his antipsychotic drugs.

Table 1. Neuropsychiatric and Adrenal Findings in 13 Cases of Adult-Onset ALD[a]

Patient Age (y)	Reference	Psychiatric Findings	Neurologic Findings	Adrenal Involvement	Neuroimaging	Course of Illness
26	Gray[11]	At age 23: change in behavior, irresponsible, stealing. At age 26: disinhibition, emotional lability, distractible, hyperkinetic	Staggering and dragging left leg for 3 weeks; hyperreflexia, bilateral extensor plantars	Hyperpigmentation, but normal corticotropin level and normal stimulation test	None	1 y later, patient incontinent of urine, increasingly more facile, emotionally labile, and disinhibited; no progression of other neurologic symptoms
21	Sereni et al[13]	Withdrawn, inattentive, anxious, violent	Left extensor plantar, severe memory dysfunction	Hyperpigmentation; corticotropin level markedly elevated	MRI: bilateral demyelination involving temporal, parietal, and occipital region right > left	6 mo after admission, developed ataxia, bilateral extensor plantars; left homonymous hemianopia; constructive apraxia; death 8 mo after presentation
16	James et al[12]	Withdrawn, poor social skills, masturbating in public	Physically clumsy, seizures	Marked hyperpigmentation of scrotum, nipples, buccal mucosa; adrenal insufficiency	CT: dilation of posterior walls of lateral ventricle MRI: extensive abnormal periventricular white matter disease; loss of gray/white matter in occipital lobes	By age 17, florid psychosis with auditory hallucinations, delusions of passivity, paranoia. At age 20, developed seizures. Decline in IQ from 75 at age 15 to 59 by age 28
48	Panegyres et al[14]	Personality changes, depression, increasingly uncommunicative, abusive, sexually aggressive, several suicide attempts	Incontinence, bilateral extensor plantars	None	CT: widespread low attenuation areas throughout the deep white matter with contrast enhancement of corpus callosum, occipital, and temporal lobes	At age 53, developed seizures and dementia and died soon after from pulmonary embolism
24	Angus et al[16]	At age 24: diagnosed with schizophrenia with delusional thoughts, hallucinations, anhedonia, self-neglect, disinhibition; treatment-resistant	None	None initially, but by age 37 corticotropin level was elevated	MRI: decreased gray/white matter contrast; multiple T_2-weighted hyperintensities in trigone and splenium of corpus callosum	At age 34, developed orofacial dyskinesia, choreoathetosis; by age 37, emaciated, deeply pigmented, with primitive reflexes, bilateral extensor plantars, disinhibition, and dementia
28	Angus et al[16]	Disturbed personality; disinhibited, loud, self-neglect	Mild spastic paraparesis	None	MRI: increased periventricular T_2-weighted signal	Unknown
20	Angus et al[16]	Personality changes, alcohol abuse, self-mutilation, suicide attempts. Diagnosis: bipolar affective disorder	None	Adrenal insufficiency	CT: normal MRI: symmetrical diffuse increase in T_1 and T_2 signal around temporal and occipital horns of lateral ventricles	Developed tonic-clonic seizures at age 25; by age 26, demented, mild spastic paraparesis, gait ataxia, peripheral neuropathy; functionally totally dependent; death 10 mo after onset of seizures
57	Weller et al[15]	Disoriented, hypomanic, marked disinhibition	Slow apraxic gait, fluent aphasia, alexia, dysgraphia, dyscalculia, right homonymous hemianopia, right extensor plantar response	None	MRI: diffuse left hemispheric demyelination involving left frontotemporal and occipital regions, also involvement of corpus callosum and cerebral peduncle	One y later, severe dementia, global apraxia, right hemiparesis, and urinary incontinence
33	Sobue et al[17] (monozygotic twins)	Mania: irritability, aggression, increased spending, restlessness, verbal outbursts, disinhibition	Fatiguability, anorexia, hyperreflexia, bilateral extensor plantars	Corticotropin level markedly elevated; significant adrenal insufficiency; hyperpigmentation	MRI: minor periventricular T_2-weighted signals	At age 31, intellectually normal; age 33, progressive cognitive impairment
32	Sobue et al[17] (monozygotic twins)	Anxiety, somatic preoccupation; quick-tempered, grandiose, profligate, belligerent, followed by depression. Diagnosis: bipolar affective disorder	None	Corticotropin level mildly elevated	MRI: extensive T_2 high intensity signal in occipital, parietal, and temporal areas; also involvement of hippocampus and cerebellum	Initially trained as a dentist; by age 36, IQ = 65; developed spastic ataxic gait, urinary incontinence, horizontal nystagmus, dysarthria, hyperreflexia, bilateral extensor plantars, and loss of vibration and proprioception in both legs

continued on next page

Table 1 (Continued). Neuropsychiatric and Adrenal Findings in 13 Cases of Adult-Onset ALD[a]

Patient Age (y)	Reference	Psychiatric Findings	Neurologic Findings	Adrenal Involvement	Neuroimaging	Course of Illness
31	Menza et al[18]	Began at age 26: substance abuse; agitated, irritable, intrusive, hyperactive, sexually inappropriate, loud pressured speech, euphoric. Diagnosis: bipolar affective disorder	Urinary and fecal incontinence; bilateral extensor plantars	Adrenal insufficiency (on replacement therapy)	CT: some ventricular enlargement	Developed cognitive impairment 6 mo later
33	Menza et al[18]	Numerous hospitalizations, alcohol abuse; depression, multiple suicide attempts, auditory hallucinations, poor impulse control, irritability, paranoid delusions, pressured speech. Diagnosis: schizophrenia	None	None	CT: ventricular enlargement with periventricular white matter lucencies	Memory impairment 2 years later; incontinent, ataxic, bilateral extensor plantars; progressive dementia
30	present case	Extensive history predating neurologic symptoms including substance abuse, psychosis with paranoid delusions, aggression, perseveration, marked disinhibition, distractibility	Wide-based, spastic, ataxic gait, right/left confusion, apraxia, aphasia, hyperreflexia, bilateral extensor plantars, primitive reflexes, urinary incontinence, peripheral neuropathy	Corticotropin level markedly elevated; abnormal corticotropin-stimulation test	CT and MRI revealed extensive white matter disease involving left and right centrum semiovale, corona radiata, and parietal regions; pinpoint signal abnormality in basal ganglia and pons bilaterally	Cognitive decline

[a]Abbreviations: ALD = adrenoleukodystrophy, CT = computed tomography.

Important clinical clues that led to further investigation and diagnostic reformulation in the present case included the failure of the patient to respond to medication and the continuing deterioration in his clinical status. Treatment unresponsiveness has received a great deal of attention in the literature, usually in the context of considering alternative pharmacologic strategies for the recalcitrant symptoms. As this case and other recent examples illustrate,[50,51] however, treatment resistance should also prompt a search for an underlying metabolic disorder. Similarly, clinical deterioration should not automatically be ascribed to medication effects or the burdens of psychiatric illness, particularly if there is cognitive decline. Intellectual deterioration can, of course, be difficult to recognize, since memory loss, confabulation, paraphasias, and word-finding problems are easy to confuse with psychosis. Formal testing of intelligence can be useful in this regard, especially if there are school records with which to compare the results.

Another lesson to be learned from the present case is the importance of regularly reassessing the neurologic and radiological findings of patients with chronic psychiatric illness. Patients whose neurologic examination and MRI scan results are normal at the time of first presentation may later develop abnormal findings. These will be missed unless a formal neurologic examination and MRI scan are repeated every few years.

Treatment Considerations

Treatment of underlying disorder. The treatment of ALD initially focused on reducing the dietary intake of certain long chain fatty acids. When this failed to alter the progression of illness,[52] alternative dietary manipulations including the use of Lorenzo's oil (a 4:1 ratio of oleic acid and erucic acid), were tried. The hope was that the competition of certain very long chain fatty acids for the microsomal elongation system that builds VLCFA would decrease their production and buildup within the cell. Unfortunately, clinical studies of Lorenzo's oil have failed to demonstrate efficacy in patients who already have neurologic involvement, although there is some evidence that presymptomatic patients may benefit from extended treatment.[53–55] Newer treatments under investigation include gene therapy and immunosuppression with cyclophosphamide, β-interferon, and thalidomide.[2]

Bone marrow transplantation is now being used for ALD patients who have not yet demonstrated clinical symptoms, but who have MRI evidence of demyelination.[56,57] The rationale for bone marrow transplantation is to provide the patient with healthy cells that have the ability to degrade VLCFA. Such an approach seems to be less effective when the individual has already developed neurologic findings. This makes the early diagnosis of this disease and genetic testing of other family members crucial.

Treatment of psychiatric symptoms. The pharmacologic treatment of patients with ALD is problematic. Not only do patients often not respond to the medications in a typical manner, but they may be extremely sensitive to the side effects.[50] In addition, there is reason to believe that treatment with neuroleptics might actually worsen the underlying pathology of ALD. Neuroleptics have been shown to inhibit oxidative phosphorylation and increase levels of free radicals in the brain.[58,59] This could, in the face of an already compromised system, decrease the ability of the brain to make adenosine triphosphate (ATP) and thus further compromise affected areas, rendering them more susceptible to the disease process. Our patient developed parkinsonism, akathisia, and tardive dyskinesia, with little relief of his underlying psychosis, over a 10-year course of neuroleptics. The parkinsonism not only masked his spasticity, but further impaired his mobility and motor function. His dysphagia was so severe that he repeatedly aspirated and developed pneumonia. Off neuroleptics, his swallowing function improved, and he gained weight. The anticholinergic medications that are typically used to treat extrapyramidal side effects pose problems of their own, as they will tend to exacerbate the cognitive impairment, dysphagia (by causing dryness), and hypotension that are often present in patients with ALD. Given the overlap between certain types of frontal lobe dysfunction and mania, it is possible that these patients would respond well to lithium, although to our knowledge this has never been studied.

Clearly concurrent substance use or abuse must be addressed with the goal of complete abstinence. It is impossible for us to know how much substance misuse was a factor in the onset and nature of our patient's psychosis. Indeed, there was never any documentation of positive blood or urine specimens or evidence of intoxication in his medical records. The psychiatric symptoms of ALD typically include silliness, personality change, impaired judgment, impulsivity, and disinhibition, which can also be characteristics of drug or alcohol intoxication. It is our experience that when there is any atypicality in the clinical presentation of psychosis and there is a suggestion of substance use, the significance of the latter may be inappropriately overestimated.

Drug names: chlorpromazine (Thorazine and others), cyclophosphamide (Cytotoxin), fluphenazine (Prolixin and others), haloperidol (Haldol and others), β-interferon (Avonex, Betaseron), lidocaine (Xylocaine and others), loxapine (Loxitane), omeprazole (Prilosec), thalidomide (Thalomid), trihexyphenidyl (Artane and others).

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