CASE 8.2
Autism Spectrum Disorder | Level 2

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1. What subjective and objective evidence supports the diagnosis of ASD?

Identified risk factors for ASD (not present in this patient) are closer spacing of pregnancies; advanced maternal or paternal age (generally ages greater than 35 years old); and extremely premature birth (less than 26 weeks gestational age).

SUBJECTIVE FINDINGS: There is a delay in or total lack of the development of spoken language—the content of her speech is comparable to that of a 24-month old. She has marked impairment in the ability to initiate or sustain a conversation with others. There is an inflexible adherence to specific nonfunctional routines or rituals, e.g., mother states, "She insists on having me tie her shoes left to right before breakfast, otherwise she will hit me!" She is more socially withdrawn from other children and has had difficulty developing peer relationships appropriate to her developmental level. There is a lack of social or emotional reciprocity; she maintains a flat affect during social interactions. She exhibits a persistent preoccupation with parts of objects, e.g., focusing on the wheels of a toy bus in the classroom.

OBJECTIVE FINDINGS: The findings on physical exam are agitation, bruising around eyes from self-injurious behavior, tachycardia, respiratory depression, and fine hand tremor.

She has a childhood autism rating scale (CARS) score of 38. Using the CARS, the cutoff for diagnosis of ASD is at least 30 for mild ASD. Scores of 30 to 37 indicate mild-to-moderate ASD and scores of 38 to 60 indicate severe ASD. Scores range from 15 to 60 for the CARS. Average sensitivity and specificity for the CARS were 89% and 82%, respectively, for autism; and 82% and 80% for ASD.

2. Assess the nonpharmacologic and pharmacologic therapy for ASD and seizure disorder.

ASD: The patient did not present with pharmacologic treatment, which would be appropriate if the patient did not present with symptoms prior to the episodes and was controlled on behavioral techniques. Pharmacologic treatment should only be considered when there is a specific target symptom (hyperactivity, inattention, impulsivity, aggression, self-injury, anxiety, obsessive-compulsive behaviors, rigidity, repetitive behaviors, and depressive symptoms) or coexisting

condition. She is currently on a casein-free and gluten-free diet. Cochrane Collaboration review of gluten-free and casein-free diets in ASDs showed significant improvements in overall autistic traits, social isolation, communication, and interaction. The report noted there were no harmful outcomes. If the parents and child feel there has been improvement on this diet, it may be continued.

MEDICATION-RELATED PROBLEM: The patient is currently presenting with signs of acute valproic acid toxicity. Her valproic acid level is 139 mcg/mL, and the symptoms she presents with are hypotension, respiratory depression, tachycardia, tremor, borderline serum ammonia levels, and agitation. However, the mother said the agitation was related to her not getting her treats. The patient is currently on 1,000 mg/day, calculated to be approximately 57 mg/kg/day. Most patients' seizures are controlled at doses below 60 mg/kg/day; however, given her symptoms and valproic acid level, she appears to be experiencing toxicity.

- ❑ Supportive care is the principal treatment for valproic acid toxicity and results in positive outcomes for the vast majority of patients. This involves management of fluid status, autonomic system control, and hemodynamic support. This would be optimally managed in the inpatient hospital setting.
- ❑ Carnitine supplementation has been shown to reduce symptoms in patients with valproic acid-induced hyperammonemia and hepatotoxicity. This may be caused in part by a carnitine deficiency to which carnitine supplementation may prevent and attenuate these adverse reactions. In this case, carnitine supplementation would not be necessary as the patient does not present with lethargy, elevated ammonia levels, or with hepatic dysfunction. However, there are no adverse reactions related to carnitine therapy for valproic acid toxicity so in the absence of clinical or laboratory signs of toxicity, oral carnitine can be administered prophylactically with a dose of 150 to 500 mg/kg per day (up to 3 g/day) divided every 6 hours given by mouth. The patient weighs 17.6 kg; thus, the appropriate dose can be rounded to 2,640 mg (8,800 mg divided every 6 hours). However, with a maximum dose at 3,000 mg (3 g), 750 mg by mouth every 6 hours would meet that maximum dose.
- ❑ Gastrointestinal decontamination would not be necessary because the toxicity was a result of chronic administration of the medication as opposed to an acute overdose.

SEIZURE DISORDER (PHARMACOLOGIC): Valproic acid requires therapeutic drug monitoring and has many drug interactions similar to other older anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin). Although the patient's seizures were controlled on this medication and valproic acid was an appropriate agent for the patient, some may be hesitant to restart this medication provided that the patient had toxicity with it. If chosen to continue this medication, hold valproic acid therapy and monitor the patient's serum level daily. Restart valproic acid at a low dose of 10 to 15 mg/kg/day (176 to 264 mg/day) once serum levels fall within normal range. A dose of 200 to 250 mg can be administered easily in the liquid formulation as doses of 4 mL or 5 mL, respectively, from the 250 mg/5 mL stock bottle. Serum levels may be monitored weekly after the patient has restarted therapy to aid in adjusting the dose to a therapeutic level. Also seizure control, liver function tests, cognitive impairment, vital signs, and neurological status should all be evaluated monthly until steady-state has been reached and may advance to every 3 to 6 months thereafter. The goal is to continue to keep the patient seizure free. As the half-life of valproic acid is 7 to 13 hours, the serum levels would be expected to drop over 2 to 3 days. Once the patient is restarted on valproic acid, the dose may be increased by 5 to 10 mg/kg/day at weekly intervals until therapeutic levels are achieved.

3. Develop an alternative plan to treat the patient's seizure disorder.

Lamotrigine, oxcarbazepine, and topiramate are three newer anticonvulsants with a more favorable drug profile than valproic acid and