with systemic corticoids is often proposed.3

We believed that nevirapine should be added to the list of drugs that can cause DRESS syndrome. The patient must be closely watched while being treated with this medication because DRESS syndrome has a mortality rate of 10% (generally because of liver involvement). Therefore, if symptoms are suggestive of DRESS syndrome, it is necessary to discontinue all treatment, and the patient should be admitted to the hospital and closely monitored for possible complications.

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Complete Resolution of Reflex Sympathetic Dystrophy With Thalidomide Treatment

Reflex sympathetic dystrophy (RSD) is a disabling syndrome of regional pain, sensory changes, and edema following a noxious event. The pathogenesis is believed to be related to an increased rate of efferent sympathetic nerve impulses toward the involved extremity induced by increased afferent activity. Thus, therapy has been aimed at interrupting sympathetic nerve activity medically, surgically, or chemically.1,2 Therapy for RSD is disappointing, and patients experience a significantly poor quality of life. We report a serendipitous dramatic resolution of RSD in a patient treated with thalidomide for recently diagnosed myeloma unrelated to her RSD.

Report of a Case. A 43-year-old woman with a history of severe RSD was seen for treatment of newly diagnosed multiple myeloma. Three years ago she developed RSD involving the left-upper and left-lower extremities following a traumatic injury to her left hand. The symptoms included atrophy of muscles of the left hand with contractures of the digits, severe attacks of neuropathic pain, and swelling. Extensive medical therapy including cervical spine fusion, 33 stellate ganglion blocks, epidural anesthetics, and placement of central and lumbar stimulation devices had failed. At the time myeloma was diagnosed, she had been unable to walk and was largely confined to a bed or wheelchair because of left-leg pain, swelling, and ulcerations occurring over 6 months. She required treatment with oxycodone hydrochloride and transdermal fentanyl citrate for pain control.

Multiple myeloma was incidentally diagnosed when a serum monoclonal IgG κ protein level of 2 g/dL was detected on routine laboratory testing. On further evaluation, anemia and a 40% involvement of the bone marrow with plasma cells was detected, and early-stage myeloma was diagnosed. After receiving her informed consent, she was enrolled in a clinical trial of single-agent therapy with thalidomide at 200 mg/d, increased to 400 mg/d after the first 2 weeks. After 1 month of receiving thalidomide treatment she had an unexpected, marked improvement and near resolution of RSD symptoms. Her leg ulcerations and edema completely healed (Figure), and she was able to discard her wheelchair and walk normally. In the next few months, she discontinued all treatments with pain medications and cervical and lumbar stimulation devices and regained function in her left hand. Myeloma responded more gradually, with a 50% decrease in serum mono-
clonal protein and bone marrow plasma cell involvement at 6 months.

Comment. Thalidomide, which was banished from clinical use in the early 1960s owing to severe teratogenicity, has now made a remarkable comeback as an effective agent in the treatment of relapsed and refractory multiple myeloma.3-5 Although the mechanism of action in myeloma is unknown, it is believed that its effectiveness may be related to its anti-angiogenic and immunomodulatory properties. The major toxic effects of thalidomide are sedation, constipation, rash, and peripheral neuropathy. The peripheral neuropathy is usually mild and occurs in approximately 30% to 50% of patients treated with the agent.3-5 The remarkable benefit observed in this patient with RSD may be related to the effect of thalidomide on afferent sensory nerves and/or efferent sympathetic nerves coupled with its anti-inflammatory properties.

There is no evidence that the plasma cell dyscrasia in this patient was related to her underlying RSD. The resolution of RSD was also likely unrelated to the response of the underlying myeloma to thalidomide therapy. The resolution of RSD occurred rapidly in contrast to the slow response in myeloma protein level over many months. Given the lack of good treatment options for RSD, we recommend that appropriate clinical trials with thalidomide be considered in this disease.

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Monoamine Oxidase Deficiency: A Cause of Flushing and Attention-Deficit/Hyperactivity Disorder?

It is not uncommon for a patient to present to a physician with the complaint of flushing. Differential diagnoses include menopause, thyrotoxicosis, medications, alcohol, carcinoid syndrome, pheochromocytoma, medullary carcinoma of the thyroid, and systemic mastocytosis.1 Sometimes no cause is identified. In this case report, we describe a family with a novel cause of flushing and diarrhea, most likely the consequence of a hereditary enzymatic defect. Such a disorder may account for some idiopathic cases of flushing and, as illustrated by our subjects, might even be a cause of attention-deficit/hyperactivity disorder (ADHD).

Report of Cases. A 42-year-old woman presented with a history of flushes, headaches, and diarrhea. From the age of 30 years, she had experienced chronic diarrhea, up to 5 to 6 times daily, with crampy abdominal pain. Gastroscopy and colonoscopy had demonstrated no abnormalities, and she was considered to have irritable bowel syndrome. At the age of 33 years, she developed migraines. These were associated with blurred vision, photophobia, tunnel vision, nausea, and vomiting. Attacks would last 3 to 4 hours and several would occur each week. She had been administered various antimigraine medications with little benefit. Flushing also developed, mainly affecting the face and upper chest. On occasions, she would turn scarlet. Episodes were precipitated by emotion, intercourse, and foods such as capsicum and wine. The flushing was generally followed by diarrhea, headache, and sometimes palpitations. She became increasingly moody and irritable.

The woman was of normal intelligence and had attended a school for gifted children. She was a nonsmoker and nondrinker. She had mild hypothyroidism diagnosed several years earlier, which was treated with thyroxine replacement. The results of her physical examination were unremarkable. Her blood pressure was 130/90 mm Hg and heart rate was 80/min. She had previously been extensively investigated for her symptoms. Full blood cell count, electrolyte levels, liver function test results, calcium level, and anti-nuclear factor were normal. Her luteinizing hormone, follicle-stimulating hormone, and estradiol levels indicated that she was premenopausal. Her urinary catecholamine and histamine levels and pentagastrin stimulation test results were normal. On screening, her serum serotonin level was elevated from 349 ng/mL (2.0 µmol/L) to 811 ng/mL (4.6 µmol/L) (reference range, <211 ng/mL [<1.2 µmol/L]) on multiple occasions throughout a number of years. Her urinary 5-hydroxyindoleacetic acid (5-HIAA) level was 5.4 mg/24 h (28 µmol/d) (reference range, <6.7 mg/24 h [<35 µmol/d]) and had never been elevated.

She had been considered to have carcinoid syndrome. However, the results of computed tomographic scans of her abdomen and chest, bronchoscopy, and OctreoScan (Mallincrodt Medical, St Louis, Mo) were normal. She had been treated with cyproheptadine hydrochloride, ranitidine, verapamil, and diazepam with little improvement. Various antidepressants were unhelpful or exacerbated her symptoms.

The affected woman had 2 sons. The eldest, aged 18 years, had temporal lobe epilepsy as a child and moderate intellectual impairment. He was prone to episodes of violence and had been diagnosed as having ADHD. In the previous 12 months, he had developed episodes of flushing, palpitations, and headache similar to his mother. On screening, his serum serotonin level was 1112 ng/mL (6.3 µmol/L) and his urinary 5-HIAA level was 0.96 mg/24 h (5 µmol/d). The second son was 16 years old. He was also diagnosed as having ADHD and had mild intellectual impairment. On screening, his serum serotonin level was 703 ng/mL (4.0 µmol/L) and his urinary 5-HIAA level was 0.38 mg/24 h (2 µmol/d). The 24-hour urinary normetanephrine (NMN) level was slightly elevated in both sons (Table).
The biochemical features in this family are consistent with an enzymatic block in the metabolism of serotonin to 5-HIAA (Figure). This suggests an inherited deficiency of monoamine oxidase (MAO).

There are no known stimulators or analogues of MAO. The woman was treated with sertraline hydrochloride because this depletes platelet serotonin. Platelets are the major storage site of serotonin in the blood, and by preventing its reuptake, we hoped to promote its renal excretion. Thus, less serotonin was available for release. The dose of sertraline was cautiously increased because of concerns about precipitating serotonin syndrome. Treatment initially resulted in some worsening of her symptoms, but subsequently the frequency of flushing and headache decreased, she felt less moody, and the diarrhea decreased. Her serotonin levels fell, and 1 year later, her platelet serotonin levels are normal at 462 ng per 10⁹ platelets (reference range, <1000 ng per 10⁹ platelets) while taking sertraline hydrochloride, 50 mg/d. One son has started treatment, and his platelet serotonin level has fallen from 2504 ng per 10⁹ platelets to 1634 ng per 10⁹ platelets while taking sertraline hydrochloride, 25 mg/d.

Comment. We have described and treated a family with clinical and biochemical features consistent with MAO deficiency. A kindred with X-linked recessive MAO-A deficiency has in fact previously been described. A point mutation was identified on the eighth exon of the structural gene for MAO-A. Affected males in this family had mild mental retardation and often violent behavior. Flushing and diarrhea, however, were not features of their disease. Also in contrast to our family, the predominant biochemical abnormality was deranged catecholamine metabolism, rather than serotonin metabolism. These differences suggest that our family may have another mutation, resulting in differential allelic expression of MAO-A. Another possibility is MAO-B deficiency, but this is unlikely because it is considered to be incompatible with life.

The elevated 5-NMA level can also be explained by reduced MAO activity, since 5-NMA is metabolized to 3-methoxy-4-hydroxymandelic acid by MAO. Abnormalities of catecholamine metabolism have been proposed to underlie the pathophysiological causes of ADHD. Although our subjects only had minor abnormalities in urinary catecholamine levels, it is possible that the degree of derangement in the cortical pathways is greater. The findings in our family raise the possibility that some cases of ADHD may be a result of MAO deficiency and would support further research into the role of MAO in the pathogenesis of ADHD.

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