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DRESS ASSOCIATED WITH PERAMPANEL ADMINISTRATION IN A CHILD WITH DRUG-RESISTANT EPILEPSY

A 13-year-old girl presented with rash and fever while vacationing in the United States. Five weeks earlier, in her home country, the United Kingdom, she began perampanel (Fycompa; Eisai, Tokyo, Japan) for treatment of drug-resistant epilepsy. Her history includes prenatal exposure to IV drugs and postnatal development of mild left hemiparesis with associated right periventricular leukomalacia. At age 9 months, she began having left-sided focal seizures. She developed an epileptic encephalopathy manifested by cognitive regression associated with continuous spike wave in slow wave sleep more prominent over the right hemisphere. Medication history included phenobarbital, rufinamide, sultiame, clobazam, lacosamide, and levetiracetam, all discontinued because of poor seizure control or toxicity. Her epilepsy stabilized on lamotrigine and valproic acid over 2 years with good control of her generalized tonic and tonic-clonic seizures. She still experienced daily breakthrough negative myoclonic seizures, for which perampanel was started, initially at 2 mg QHS, increasing to 4 mg QHS after 4 weeks.

One week after the increased dose, the patient developed a temperature of 39°C, a cough, and a lower extremity erythematous rash. She became increasingly lethargic, and 1 week later presented with a generalized erythematous and petechial rash, facial swelling, and hypotension. Laboratory studies showed an elevated leukocyte count of $52 \times 10^9/L$ without eosinophilia, acute renal failure, increased liver enzymes, a perihilar infiltrate on chest x-ray, and normal results on CSF examination. CT scan was at baseline, showing generalized brain atrophy with moderate dilation of the right lateral ventricle suggesting underlying volume loss. Given concern for septic shock or Stevens-Johnson syndrome, she was started on antibiotics. Blood, urine, and CSF cultures were negative. She developed hypotension and acute respiratory distress syndrome and required multiple vasopressors, blood product transfusions (fresh-frozen plasma, albumin, packed erythrocytes), and mechanical ventilation. She also developed oliguria, a profound metabolic acidosis, and an elevated C-reactive protein. She had prominent lesions around the nose

and lips with xerosis, desquamation, and generalized erythroderma with superficial exfoliation, but with a negative Nikolsky sign and no skin sloughing or bullae. A skin punch biopsy found superficial perivascular and interstitial lymphocytic/eosinophilic infiltrates, leading to a diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS), likely precipitated by perampanel. All antiepileptic drugs were discontinued and methylprednisolone was started. Given low immunoglobulin G levels, IV immunoglobulin was administered. Within 2 days, her erythroderma and renal and hepatic function improved and vasopressors were discontinued. Continuous EEG captured frequent parasagittal epileptiform discharges, which were controlled by levetiracetam. Within 5 days of discontinuing perampanel, she was extubated and her steroid dosages lowered. She was hospitalized for 3 weeks, her neurologic function returned to baseline, and she was discharged home with supplemental oxygen, levetiracetam, and a 6-month-long steroid taper, to be followed by her neurologist.

Discussion. This is the first reported case of DRESS attributed to perampanel. DRESS is a severe idiosyncratic adverse drug-induced reaction that is difficult to diagnose due to its clinical heterogeneity and its similarity to other syndromes.¹ The pathogenesis of DRESS has not been fully clarified, but genetic predisposition and viral reactivation are proposed mechanisms. While no international consensus exists for clinical diagnosis, fever and a severe skin eruption are the first and most common signs, with hematologic abnormalities (eosinophilia or atypical lymphocytes) and internal organ involvement (renal, hepatic, or cardiovascular) typically required to solidify the diagnosis.² Onset is characteristically delayed from initiation of drug therapy by 2 to 6 weeks.¹

Perampanel is a first-in-class orally active, non-competitive amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor antagonist.^{3,4} Side effects in phase III studies were mild to moderate, and analysis of pooled data concluded that safety and tolerability were acceptable.⁵ In 2012, the European Union approved usage for adjunctive therapy in partial-onset seizures (for patients age >12 years), with US

approval following in 2013.⁶ Perampanel has a long half-life (105 hours), is protein-bound, and is primarily metabolized via the P450 enzyme CYP3A4. Perampanel neither inhibits nor induces the cytochrome system, and its reduction of clearance of valproate and lamotrigine is reported to be <10%.⁷ Conversely, P450 inhibitors/inducers may affect perampanel levels. Valproate, a P450 inhibitor, could cause higher perampanel levels, so concurrent use may warrant more cautious dosing when initiating perampanel. Perampanel use is in its nascence, but should a patient present with fever and rash, DRESS should be considered. Mortality can reach 20% in severe cases of DRESS; thus early recognition is crucial to initiating life-saving interventions, chiefly the immediate cessation of the offending agent.²

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PRIMARY PROGRESSIVE NARCOLEPSY TYPE 1: THE OTHER SIDE OF THE COIN

Narcolepsy type 1 (NT1) is characterized by hypersomnolence associated with early occurrence of REM sleep (i.e., sleep-onset REM periods [SOREMP]) and cataplexy (i.e., sudden loss of muscle tone evoked by emotions), or with CSF hypocretin-1 (CSF hcrt-1) low levels (below 110 pg/mL, undetectable in most cases). Compelling evidence indicates that NT1 is caused by an autoimmune disease affecting HLA-DQB1*06:02 carriers.¹ Diagnostic workup requires a history of cataplexy and multiple SOREMP at sleep studies (nocturnal polysomnography and multiple sleep latency test [MSLT]) or CSF hcrt-1 deficiency.² At diagnosis, most patients with NT1 already have very reduced CSF hcrt-1 levels. Hypersomnolence and cataplexy presumably become evident when hypocretin cell loss is above 85%–90%, according to postmortem studies.³ A rapid and dramatically severe picture has been documented often in childhood-onset NT1, but it is also commonly recalled by history taking that the disorder can also slowly progress, and sleepiness may anticipate cataplexy by years. In full-blown NT1 cases, CSF hcrt-1 tends to maintain stable values through the disease course, and in only one case has CSF hcrt-1 been documented by chance before and after

development of NT1, showing an abrupt step down from normal to pathologic values when the disease occurs.⁴ We document in an adult patient the slow onset of CSF hcrt-1 deficiency paralleled by a slow clinical progression to clear-cut NT1.

Case history. A 45-year-old woman presented with hypersomnolence, daily hypnopompic hallucinations, sleep paralysis, and frequent nightmares since age 39. Despite objective evidence of intermediary CSF hcrt-1 levels (128 pg/mL), and SOREMP at both spontaneous daytime naps and nocturnal sleep during ad libitum 24-hour recording, due to the lack of SOREMP at MSLT the case fit with the diagnosis of idiopathic hypersomnia according to current nosography (table).² Brain MRI had normal results, and human leukocyte antigen typing was positive for the DQB1*06:02 allele. Modafinil was titrated up to 400 mg with temporary hypersomnolence improvements, despite regular, unchanged, sleep-wake habits. At age 43, hypersomnolence qualitatively changed with appearance of unpredictable daytime sleep attacks together with disruption of nocturnal sleep. Repeated MSLT (after 2 months of drug withdrawal) disclosed a shorter sleep latency with 3 SOREMP (table), pointing to a clear-cut diagnosis of narcolepsy type 2 (NT2).² Modafinil was re-instituted at doses up to 400 mg/day with only partial