

Case Report

Ethosuximide induced lupus-like syndrome in a 6-year-old: a case report

Ruth K. Rosenblum^{1*}, Rashmi Kirpekar², Ronald W. Jimenez², John Sum²

¹Departments of Nursing and Pediatrics, San Jose State University, San Jose, California, USA

²Department of Pediatrics, Santa Clara Valley Medical Center, San Jose, California, USA

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*Correspondence:

Ruth K. Rosenblum,

E-mail: ruth.rosenblum@sjsu.edu

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ABSTRACT

Ethosuximide has been used as an effective anticonvulsant for absence seizures for a half century. Risk of development of drug-induced lupus-like syndrome with anticonvulsants is considered to be very low and has been seldom reported. We describe a 6-year-old girl with absence seizures who developed symptoms following 6 weeks of treatment with ethosuximide. Onset of symptoms, including arthralgia, myalgia, rash and fever, were initially diagnosed as parvovirus or chronic parvovirus. Serology subsequently indicated drug-induced lupus-like syndrome although a positive double strand DNA made the diagnosis more complex. Ultimately, the girl demonstrated a dramatic improvement in symptoms following discontinuation of the ethosuximide. This case highlights the importance of excellent diagnostic skills, collaboration between primary and specialty care, and being prepared to identify an unlikely diagnosis.

Keywords: Absence seizures, Drug-induced lupus, Ethosuximide

INTRODUCTION

Ethosuximide is frequently used to treat young children with absence seizures. It is often used in children as a first-line anticonvulsant because it lacks the potential for hepatotoxicity that is present with valproic acid, and other severe side-effects noted with lamotrigine. It is tolerated well by many children, with stomach discomfort occasionally identified as an adverse effect. This is usually managed by dose titration; sometimes a different medication is indicated if symptoms are sufficiently unpleasant. The risk of developing lupus-like syndrome is considered very low with ethosuximide.¹ Anticonvulsants that have been identified as possibly inducing lupus include lamotrigine, carbamazepine, zonisamide, and valproic acid.²⁻⁴ Lupus-like syndrome is associated with more than 90 different medications; these will not be discussed here.⁵ Certain drugs cause a “loss of tolerance to self” and may trigger cross-reactive antibody reaction leading to recognizable lupus-like symptoms and serology. We report a case of ethosuximide-induced lupus-like syndrome in a 6-year-old female child.

CASE REPORT

A 6-year-old girl (MR) presented with a 6 months history of staring spells which interfered with school performance and which were increasingly unsettling to her. An electroencephalogram (EEG) showed high amplitude 3-4 Hz generalized spike and wave activity on sleep and with hyper ventilation that is occasionally associated with a clinical seizure. Isolated generalized spikes and sharp slow waves were noted, especially with sleep. Findings were consistent with primary generalized epilepsy. After EEG, treatment was initiated with ethosuximide, titrated to a dose of 250 mg BID (20 mg/kg/day). Initially, she had some minor stomach upset which resolved after discussion of taking food and medication together. Seizures dramatically improved, from a baseline of 15/day prior to medication initiation, to an occasional seizure when tired. Past medical history was unremarkable for any other medical conditions, surgeries or allergies. There is no known family history of autoimmune disease.

Two months following ethosuximide initiation, MR presented to the urgent care clinic with new itchy rash on face, forehead, and behind ears. Had visited a lake the prior weekend and was also sneezing. Mom concerned about seasonal allergies. She had no history of allergies, no recent insect bites, no sick contacts, and no fever, vomiting, or diarrhea. Ethosuximide dose had been increased slightly 2-3 days previous to optimize seizure control. Physical examination indicated erythematous cheeks, blanching, a few raised papules to central cheeks, and faint lacy rash on abdomen and upper arms. Exam was otherwise unremarkable. Diagnosis of parvovirus infection was made, though indicated that if symptoms do not resolve in 3-4 days to consider medication reaction. Reassurance was given to the family, and explained that disease progression would expect development of fever that can be treated symptomatically. Seizure frequency was much better, and school performance showed improved attention in class; more importantly, she no longer had the unnerving feelings from anticipating and having an absence seizure.

Ten days following the parvovirus diagnosis, MR returned to the clinic with knee, ankle, and wrist aches, fatigue, fever and diaphoresis. Mom stated that MR was very tired and needed to nap daily after school that was unusual for her. Fever was daily with a maximum temperature of 101.9. In addition, seizure control was reduced with more frequent episodes. Initial labs including complete blood count with differential, antinuclear antibodies (ANA), erythrocyte sedimentation rate (ESR), urinalysis, electrolytes were done. Ethosuximide continued pending lab results. 4 days later, was seen again in urgent care with new symptoms of back pain, eye redness, and headache. There was no change in the previously mentioned rash, and no further increase in seizure activity. No back injury or trauma was reported, and it was not related to soccer play. Tylenol was providing some symptomatic relief. A recommendation was made to use ibuprofen around the clock for symptomatic relief, rather than steroids, for the short-term while lab results were pending.

The following week MR returned to the clinic and was much improved, although was still receiving around the clock ibuprofen every 6 h. When mom tried to extend to every 8 h, the fever would increase to 102, however joint aches and general discomfort were much improved. Ethosuximide was weaned to 250 mg each morning by mom; seizure frequency was increasing accordingly with more episodes

later in the day. At this point, ethosuximide was weaned slowly, and a prescription for valproic acid was given to the family. After having researched valproic acid, the family was hesitant to initiate it and was more comfortable with an increased seizure frequency than trying another medication with known, potentially severe side effects. Additional labs were ordered including: C3, C4, antihistone antibody, and double strand DNA.

Nephrology clinic visit and lab interpretation

MR was seen in the renal clinic a month after the onset of symptoms to rule out renal involvement due to Lupus. Ethosuximide had been discontinued for about a week prior at the time of the visit. Symptoms were much improved, joint pain had subsided, she was afebrile and her appetite and physical activity were gradually returning to normal. Parents denied any gross hematuria, facial or pedal edema. Physical examination was unremarkable. Blood pressure was normal, and height and weight were in the 50th percentile. Laboratory evaluations at that point included a lupus panel, liver function tests and urine protein and creatinine ratio (Table 1).

Serum electrolytes including blood urea nitrogen were normal with a serum creatinine of 0.4 mg/dl. Urinalysis showed trace blood, but urine microscopy showed no red blood cell/HPF, thus no true hematuria and no proteinuria. Additional laboratory evaluations pertaining to the lupus-like illness included complete blood count, ANA, anti-DS DNA, complement levels, anti-histone antibodies, anti-Smith (anti-SM)/anti RHO. ESR was 49 mm/h.

Although MR's condition had returned to baseline with complete resolution of symptoms including fever, joint pain, fatigue, rash, back pain, red eyes, her seizure frequency had increased to the pre-medication occurring 20/day. She was on no anticonvulsants for 1 months after discontinuing ethosuximide with parental hesitation to start any other anticonvulsant. Ultimately, parents agreed to start valproic acid at a very small dose.

DISCUSSION

The primary care perspective

In the days when some infectious diseases were referenced as single digits, fifth disease would be considered by any

Table 1: Selected lab results.

Result	3/27/2014	3/31/2014	4/3/2014	6/19/2014
Antinuclear antibody titer	1280			320
Antinuclear antibody pattern	Homogeneous			Homogeneous
ENA anti-SM/RNP	<1.0			<1.0
ENA anti-SM	<1.0			<1.0
Anti-DS DNA Ab <25.0 IU/mL			181.5	4.8
Complement C'3 90-180 mg/dL		78	91	99

ENA: Extractable nuclear antigens, RNP: Ribonucleoprotein, Anti-SM: Anti-Smith

pediatric provider a “no brainer” diagnostically, however, with due acknowledgment to Dr. Theodore Woodward, Pediatrics has its own small zebras. ([http://en.wikipedia.org/wiki/Zebra\(medicine\)\)](http://en.wikipedia.org/wiki/Zebra(medicine))).⁶ Part of the classic presentation of roseola, caused by parvovirus B19, is the typical facial⁶ exanthem, erythema infectiosum, or “slapped cheek” preceded by a prodrome of fever, coryza, headache, nausea and diarrhea. Facial rashes may vex the pediatrician when they are associated with findings not otherwise typical in roseola, and herein may lie a primary care lesson. Lupus might be considered whenever a facial or malar rash is encountered. Such “stripes” can help delineate a differential diagnosis, which may support the casting of a broader net. Arthralgia, as in MR’s case, may have been the first indication that the differential diagnosis might have needed to be broadened or reconsidered. The joint involvement of parvovirus is typically encountered in the small joints of the extremities, the knees and feet. In contrast, MR, during her illness, reported back pain with thoracic para-spinal tenderness and a full range of motion found on one examination. MR did not report gastrointestinal or cardiac-related symptoms and no hematologic findings of significance were evident during the course of the illness.

The question should then be posed for the primary care provider, “what signs might have helped to differentiate possible parvovirus infection from drug-induced lupus?” Certainly the lack of the rash on any extremities and the nature of the reported arthralgia may have offered supportive direction for thinking more broadly diagnostically. Laboratory studies would generally not be indicated in suspected roseola except where thrombocytopenia or neutropenia may be considered. In the case of MR, the addition of some serologic studies (e.g ANA, C3, C4) further supported the diagnosis. More extensive immunologic testing was subsequently performed. In this case, thinking more broadly about the possible causes of a parvovirus-like illness, including drug-related rashes, might have permitted the primary care provider to hear the small hoofbeats of this zebra.

The renal perspective

Although drug-related lupus (DRL) and idiopathic lupus (IL) may be clinically similar, there are no specific tests to differentiate the two. There is considerable variability in specific serologies among different drugs as well as individual differences among patients. Positive ANA is present in almost all the patients but is not specific. Antihistone antibodies are consistently elevated in drug-related lupus, Anti-DS DNA while specific for IL is usually not seen in drug-related lupus except due to hydralazine. Similarly, complement levels are normal in drug-related lupus and depressed in IL with some exceptions.⁷ Anti-SM and anti-RHO antibodies are typically negative in drug-related lupus and positive in IL. Similarly C-reactive protein is elevated in IL but not in drug-related lupus.

With MR in the absence of any renal involvement, presence of antihistone antibodies, positive ANA, negative anti-SM and anti-RNP was consistent with DI. However, presence of low complement C3 and C4 levels, positive anti-DS DNA, favored IL. The most important clinical feature suggestive of drug-related lupus was disappearance of her symptoms after withdrawal of the medication. On follow-up 3 months later, lupus serologies had improved significantly with normalization of complement levels, reduction in her ANA and antihistone titers, and disappearance of anti-DS DNA antibody, further supporting the diagnosis of drug-related lupus. The antihistone antibodies may persist for several months to years without reflecting active disease process. Non-recurrence of her symptoms in the future is further indication that likely suggest that this episode was due to drug-related lupus and not IL that is in remission for now.

Drug related lupus-like syndrome

Classification or diagnostic criteria for drug-related lupus-like syndrome does not exist at present. Sarzi-Puttini, *et al.*⁸ offer the following guidelines which are commonly used: (1) duration of treatment with the suspected drug has been at least 1 month, usually longer, (2) symptoms or organ involvement includes arthralgia, myalgia, fever, serositis, and rash, (3) ANA and antihistone in the absence of other antibody specificities, (4) improvement of symptoms within days or weeks of drug discontinuation. Although symptoms generally resolve quickly, serological abnormalities may persist for several months and should be followed. However, there is no evidence that a patient with drug-related lupus-like syndrome will develop further lupus symptoms nor ever meet the diagnostic criteria for lupus. Mechanisms of action for these phenomena are unknown. Katz and Zandman-Goddard³ postulate that drug metabolites may act as haptens for a T-cell response. Another thought is that the drug may non-specifically activate lymphocytes that can disrupt immune function. The third premise is that drug metabolites can be cytotoxic and trigger cell death in a non-immune-mediated process. This is less likely in the case report discussed here. Last, recent literature has identified biologicals such as tumor necrosis inhibitors and interferons as likely new agents for this syndrome.

CONCLUSION

This case illustrates the trajectory of a child who initially presented with straightforward absence seizures, was started on an appropriate anticonvulsant, and subsequently developed likely drug-induced lupus-like syndrome. Although the exact incidence of this phenomenon is not known, it is considered to be rare with ethosuximide, and more common with isoniazid, hydralazine, and procainamide. Occurrence in children is quite unusual. Following laboratory results and examining the evidence-based literature, we concluded that MR experienced drug-related lupus.

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