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Response to immunotherapy in a patient with Landau-Kleffner syndrome and *GRIN2A* mutation

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ABSTRACT – Landau-Kleffner syndrome (LKS) has been demonstrated in the past to respond to immunotherapy. Recently, some cases of LKS have been shown to be secondary to glutamate receptor (*GRIN2A*) mutations. Whether such cases respond to immunotherapy is not known. Here, we present the case of a 3-year-old boy with LKS found to have a *GRIN2A* heterozygous missense mutation, whose clinical symptoms and EEG responded to a course of combination oral steroids and monthly infusions of intravenous immunoglobulin. He then relapsed after discontinuation of this therapy, and responded again after a second course of intravenous immunoglobulin. We conclude that immunotherapy should be considered as a therapeutic option in patients with LKS who are also found to harbour *GRIN2A* mutations.

Key words: epilepsy, speech regression, electrical status epilepticus in sleep (ESES), NMDA 2A receptor

The *GRIN2A* gene encodes for the glutamate receptor, ionotropic, N-methyl-D-aspartate (NMDA) 2A. Dysfunction of this NMDA receptor has recently been linked to various forms of epilepsy, including Landau-Kleffner syndrome (LKS), and atypical rolandic epilepsy (Carvill *et al*., 2013; Lesca *et al*., 2013; DeVries and Patel, 2013). LKS occurs in previously normal children, and presents with isolated regression of language, auditory agnosia, and at times focal seizures and behavioural problems. The EEG pattern shows epileptiform discharges, usually over the temporal lobes, which increase during slow-wave sleep. Treatment includes a number of antiepileptic drugs, immunotherapy using various corticosteroid medications and regimens, and occasionally intravenous immunoglobulin (IVIG) (Mikati *et al*., 2002; Gallagher *et al*., 2006; Geva-Dayan *et al*., 2012). In addition, there is a significant body of evidence linking LKS to abnormal autoimmunity (Nevsímalová *et al*., 1992; Connolly *et al*., 1999; Boscolo *et al*., 2005). However, whether cases of LKS caused by *GRIN2A* mutations respond to immunotherapy is not

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known. Here, we report a case of LKS with a *GRIN2A* gene missense mutation in which the patient was responsive to immunotherapy.

Case study

History before immunotherapy

The patient was the product of full-term gestation without newborn complications. Parents reported normal motor and speech development until 2 years of age. Family history was positive for a brother with attention deficit disorder, speech delay, and apraxia, as well as for a cousin with attention deficit disorder and seizures.

At 22 months of age, the patient was hospitalized for a one-week history of progressive clumsiness and frequent falls following a flu-like illness. At that presentation, he was ataxic on examination, and workup, consisting of brain MRI, basic CNS analysis, and urine drug screening, was unremarkable. He was discharged home with the diagnosis of acute post-infectious cerebellitis and the ataxia resolved over the following month.

At 2 years of age, the patient was readmitted for gait changes and seizures which consisted of clonic activity in the right arm and leg. At that time, his speech development was normal; he could form two- to three-word phrases. EEG revealed multifocal parietal and centro-temporal sharps and right frontal epileptiform discharges with marked increase in discharges when drowsy and asleep. Levetiracetam was started and over the next few months, the patient underwent prolonged EEG monitoring to characterize further events possibly related to seizures. EEG was abnormal, as noted earlier, but no events or subclinical seizures were captured. Upon turning 3 years of age, he appeared to have normal language development with the use of three- to four-word phrases.

At 3 years of age, the patient's speech output regressed to using only one- to two-word phrases and he became unable to understand first complex and later simple commands. EEG at the time showed bi-hemispheric spike-wave discharges with a 56% spike-wave index in sleep and 42% during wakefulness. Diazepam was started at a dose of 10 mg per day (0.7 mg/kg/day), after which his language and mood returned to baseline over several weeks with a corresponding resolution of the EEG discharges. Five months later, the patient was weaned off diazepam but his language regressed again. EEG showed recurrence of nocturnal spike and wave discharges, so diazepam was re-initiated at prior dosing and resulted in an incomplete clinical improvement with relapses during further attempts to taper diazepam. Long-term EEG monitoring continued to be abnormal with multifocal spikes and met criteria for electrical status epilepticus in sleep (ESES).

In the subsequent months, his speech failed to improve despite speech therapy. At the age of 3 years and 11 months, he was only able to speak in one- to two-word sentences. His neurological examination at the time was also remarkable for diffuse hypotonia, as well as lack of motor coordination.

Immunotherapy and response

The patient was started concurrently on a six-month steroid course of prednisone at 30 mg/day (tapered toward the end of the course) and on IVIG therapy, with an initial 2 g/kg dose, then 1 g/kg monthly, during the same six months. He was also maintained on the same prior doses of levetiracetam and diazepam without change. His speech gradually improved over the six months of therapy. By the sixth month of therapy, he was able to produce 10-word sentences and could recite all letters of the alphabet and answer questions in clear and well-articulated sentences.

Following cessation of the above IVIG and prednisone therapies, his speech again regressed over a period of several weeks while still on levetiracetam and diazepam therapies. He was able to only use three-word sentences and was unable to follow any commands. Continuous video-EEG monitoring showed diffuse slowing, multifocal bilateral spikes, and near-continuous (>85%) ESES.

Based on his worsening clinical status and EEG results, IVIG therapy was re-initiated about eight weeks after the cessation of the above therapy, using the same protocol as stated above but without steroids. Over the following three months, he regained his speech abilities and was back to using seven-word sentences, as well as following simple and complex commands. A repeat EEG showed only rare sharps during sleep.

Workup

An extensive diagnostic evaluation was initially unremarkable. It included brain MRI/MR spectroscopy, testing for inborn errors of metabolism, extensive CSF analysis including neurotransmitters, as well as an autoimmune workup that included CSF analysis and autoantibody testing.

The patient ultimately underwent whole-exome sequencing which revealed a missense mutation in the *GRIN2A* gene: c.2146G>A, p.Ala716Thr (A716T). This mutation has been previously reported in a family with atypical rolandic epilepsy, verbal dyspraxia and cognitive impairment (Lesca *et al*., 2013), and was not observed in approximately 6,500 individuals of European and African American ancestry in the NHLBI Exome Sequencing project. The change alters a highly conserved position in the extracellular domain of the

protein and in-silico analysis predicts that it is likely damaging to the protein structure and function. Both his parents and brother were tested and did not have this *GRIN2A* missense mutation.

Discussion

Our patient fulfilled the criteria for LKS (Berg *et al*., 2010) and had a *GRIN2A* missense mutation predicted to be disease-causing based on the following:
– the same c.2146G>A mutation was previously reported in a family with atypical rolandic epilepsy, verbal dyspraxia, and cognitive impairment (Lesca *et al*., 2013);
– this mutation was not observed in approximately 6,500 individuals of European and African American ancestry in the NHLBI Exome Sequencing project;
– it is a non-conservative amino acid substitution that is probably damaging to the protein structure and function based on in-silico analysis;
– his parents and his brother did not have this change.
Our patient responded to immunotherapy. Response was remarkable and occurred on two different occasions with a relapse in between when immunotherapy was stopped after the initial six months of therapy. Apart from the aforementioned genetic cause of LKS, there is reasonable evidence that at least some cases of LKS may have an autoimmune aetiology. Autoantibodies to myelin (Nevsímalová *et al*., 1992), to CNS endothelial cells (Connolly *et al*., 1999), and to rat brain auditory cortex (Boscolo *et al*., 2005) have been found in children with LKS. Moreover, LKS has been linked to other disorders of autoimmunity, including inflammatory demyelinating disease (Perniola *et al*., 1993) and cerebral arteritis (Pascual-Castroviejo *et al*., 1992). LKS has been found to respond to both steroids and IVIG (Mikati *et al*., 1998, 2000, 2002, 2010; Gallagher *et al*., 2006; Geva-Dayan *et al*., 2012). In our patient, an autoimmune aetiology was suspected, not only due to his response to immunotherapy, but also due to his history of possible cerebellitis following a flu-like illness.
Since only a fraction of patients with LKS respond to immunotherapy, it is reasonable to suspect that some LKS patients may have an underlying autoimmune aetiology, while patients with LKS secondary to a genetic cause, such as a *GRIN2A* mutation, may not have an underlying autoimmune aetiology. In this article, we present evidence that at least in some cases this may not be the case; our patient's *GRIN2A* mutation likely contributed to his disorder, but he also responded to immunotherapy. We thus posit that the presence of a mutation predicted to be disease-causing should not prevent attempts to treat with immunotherapy, especially in patients with epilepsy and speech regression that has been refractory to other treatment modalities.
Indeed, prior observations in humans and in animal models have demonstrated that genetic and non-genetic aetiologies may both contribute to an epileptic syndrome (Choueiri *et al*., 2001; Leonard *et al*., 2013; Diamond *et al*., 2014). This, and our observations, can thus serve as a reminder to the epileptology community that determining one aetiology, such as a disease-causing mutation, is not necessarily the end of the quest to delineate the cause of an epilepsy.
Our observations have two potential implications that warrant investigation in future studies. First, patients with *GRIN2A* mutations should be considered for immunotherapy in future studies of therapy for this disorder. Second, in LKS associated with *GRIN2A* mutations, an autoimmune mechanism may be a component of the underlying disease process. A possible hypothesis is that the mutation itself may increase the antigenicity of the extracellular component of this particular NMDA receptor. This may especially be the case in patients with prior evidence of a possible autoimmune process (*e.g*. acute post-infectious cerebellitis) and subsequent epilepsy. Furthermore, the epileptic process itself may contribute to and enhance the autoantigenicity of the NMDA receptor, which may already be dysfunctional as a result of the *GRIN2A* mutation. This notion is consistent with the prior incisive formulation postulated by Hirsch *et al*. (2006), many years before the discovery of the association with *GRIN2A* mutations, that genetic predisposition to LKS could be related to hyper-excitability and synchronization of inter-neurons within the perisylvian cortices, which could in turn provoke an autoimmune reaction. These hypotheses would need to be investigated in future studies.
We conclude that, given the guarded prognosis for patients with LKS and our experience with this child, patients with LKS and *GRIN2A* mutation may be candidates for immunotherapy. Thus, the presence of *GRIN2A* mutations should not preclude the consideration of steroids and/or IVIG as potential therapies. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to disclose.

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TEST YOURSELF

(1) What are the cardinal features of Landau-Kleffner syndrome?

(2) What treatments are used in Landau-Kleffner syndrome?

(3) What is the function of the *GRIN2A* gene and what epileptic disorders are associated with it?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".