Summary

The numerous etiologies of refractory epilepsy include congenital cortical malformations, cerebral ischemia, post-traumatic lesions, metabolic, vascular and systemic immune diseases. Abnormal antibodies have been found in association with different types of neurological diseases and syndromes, including epilepsies. However, their frequency in the pediatric epileptic population is unknown. This study aims at knowing if, and how frequently, some of these antibodies are implicated in pediatric refractory epilepsies.

Key words: Refractory epilepsy, children, autoantibodies

Introduction

The etiologies of refractory epilepsy, defined as “a failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules [whether as monotherapies or in combination] to achieve sustained seizure freedom” [1] are numerous. These include congenital cortical malformations, cerebral ischemia, post-traumatic lesions, metabolic, vascular and systemic immune diseases. Abnormal antibodies have been found in association with different types of neurological diseases and syndromes, including epilepsies. For some of them the exact pathogenic mechanisms remain to be demonstrated, but a direct role of the antibodies in the genesis of seizures is strongly suspected. The most frequent or recently reported antibodies in association with seizures are directed against the various following targets: NMDA receptors [2, 3], Glutamic acid decarboxylase (GAD) [4], GABA receptors [5], AMPA receptors [6], and voltage-gated potassium channels [7] or, more specifically for the latter, leucin-rich glioma inactivated 1 protein-LGI1, and contactin-associated protein 2-Caspr2 [3, 8, 9]. In epilepsy series, 10 - 15% [10] of patients harbour one of these highly disease-specific autoantibodies, depending on...
how pre-selected they are (Bien C, Lang B and Vincent A, unpublished results). In that perspective, complementary treatments, such as anti-inflammatory agents, may be more readily used in pharmacoresistant epilepsies, leading to a more efficient approach than antiepileptic drugs alone. In that sense, some epilepsies previously thought to be intractable, may in fact well be controllable. Most of the published reports concern adult patients and the frequency of these antibodies in the pediatric epileptic population is unknown. This study will aim at knowing if, and how frequently, some of these antibodies are also implicated in pediatric refractory epilepsies.

### NMDA-receptors

Antibodies against NR1-NR2 heteromers of the NMDA-receptor have been reported in a form of reversible acute encephalitis in adults and in children [2, 11-14]. These patients typically present with psychiatric symptoms and cognitive difficulties, and most also have various types of seizures, dyskinesias, autonomic instability, central hypoventilation and sleep dysfunction. All gender and age categories may be concerned. The largest series in children concerns 32 patients aged less than 18 years [11]. In women, these antibodies are frequently found in association with ovarian tumors, but this seems less likely to be the case in girls [11]. In addition to the presence of serum or CSF antibodies that react to extracellular epitopes of NR-1, these patients frequently exhibit CSF oligoclonal bands and pleocytosis, focal or diffuse abnormalities on the EEG, and some of them have abnormal signals on cerebral MRI FLAIR sequences [11]. Most patients recover completely in parallel with a drop in the serum antibody titer that follows tumor removal or immune treatment [2, 11].

### Glutamic acid decarboxylase (GAD)

Glutamic acid decarboxylase (GAD) is implicated in the anabolism of γ-aminobutyric acid (GABA), the most important cerebral inhibitory neurotransmitter. This enzyme is expressed in GABAergic neurons, as well as in pancreatic beta-cells. In addition to their role in type 1 diabetes mellitus (T1DM), anti-GAD antibodies are associated with various neurological conditions, such as epilepsy [15], stiff-person syndrome [16], cerebellar ataxia, limbic encephalitis, and myasthenia gravis, all mainly described in adults [4, 17, 18]. The two most complete observations in children do not contain long-term follow-up [19, 20]. The direct pathogenicity of anti-GAD antibodies is still debated, mainly because GAD is an intracellular enzyme, barely accessible by an extracellular molecule. However, as stated by Liimatainen et al., the "intrathecal synthesis of anti-GAD antibodies may be a marker of an ongoing immune response and could be useful in identifying those patients in whom a trial of immunosuppressive therapy might be warranted" [21]. In addition, low cortical GABA levels were recently reported in association with anti-GAD antibodies [22]. The prognosis of epilepsies in such situations seems rather unfavorable, but this remains to be formally demonstrated.

### AMPA receptor, Gamma-aminobutyric acid (GABA_b) receptor and Voltage-gated potassium channel (VGKC) / LGI1-Caspr2

Various manifestations of autoimmune limbic encephalitis associated with antibodies to the AMPA receptor [6], to extracellular epitopes of the GABA_b receptor [5], or to LG1 and Caspr2 (in voltage-gated potassium channels) [8, 9], have been recently described, including in a few pediatric cases [23], some of which presented with various types of cancer. In the majority, immune therapy improved their clinical status. It is currently unknown how frequently these antibodies occur in children with refractory epilepsies.

### Hypothesis and objective of the study

Abnormal autoantibodies are probably more frequent in children with refractory epilepsies than previously thought. We plan to search for certain of these antibodies in such children on a regular basis to verify our hypothesis. Like in adults, detecting a potential immunological etiology in such situations may have major management implications for the patients. With approximately 15000 epileptic children in Switzerland (Swiss League Against Epilepsy), we estimate that 4500 children are refractory to medical treatments and as such, represent potential candidates to enroll in the study.

### Methods

The study protocol is ready to be submitted to our local ethics committee. We hope to start enrolling patients during the fall of 2011. All children with refractory epilepsies need neuropediatric care. We therefore plan to collaborate with the physicians of the Pediatric Neurology Units in Swiss Children’s Hospitals for reporting cases, most of which have already agreed to participate on the principle. In addition to the presence of abnormal antibodies, prospective data regarding EEG, MRI, neurological and developmental examination, as well as treatment will be collected.

All laboratory analyses will be performed at the laboratory of Dr C. Bien, Bielefeld-Bethel, Germany. The patients will be screened for the presence in their serum of abnormal autoantibodies. According to standard
practice, those positive for one of these antibodies will undergo a lumbar puncture to verify their conjoint presence in the cerebrospinal fluid (CSF). In these cases, CSF will also be tested for oligoclonal bands, cells, and standard chemical values. Those with a specific personal history for other autoimmune diseases will be checked for additional antibodies.

The EEGs and MRIs of these patients, performed as part of the standard management in such situations, will be analyzed in details, and repeated according to clinical evolution.

Clinical significance

We believe that autoimmune epilepsy is under-diagnosed in pediatric children. In the proposed study we would like to determine their relative frequency and follow these children during their clinical evolution. This is particularly important with regards to the proposed immuno-modulatory treatments and their efficiency, given their potential side effects. We expect to increase our therapeutic armamentarium, use it in a more targeted fashion and provide a more precise prognosis for the different autoimmune syndromes. Hopefully, at the end, we will have our own “Swiss experience” to be shared with our colleagues in and outside Switzerland.

References

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