Neuronal Surface Antibody Syndrome: A Review of the Characteristics of the Disease and Its Association with Autoantibodies

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Keywords

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Abstract

Several studies have certified that autoantibodies play an important role in the manifestation of neuromuscular diseases. Scientists have discovered specific neuronal tumor antibodies in patients with typical paraneoplastic neurological disorders. But in some clinical cases, it is not useful to cure this disease with common treatments unless the autoantibodies are addressed. In addition, recent studies have shown a close relationship between certain antibodies and neuronal surface proteins in some special cases. These antibodies, which act on the surface of neurons, mainly include voltage-gated calcium channel (VGKC) antibodies. VGKC antibodies are further divided into several types including anti-leucine-rich glioma inactivated 1 (LGI1), anti-contactin-associated protein-like 2 (Caspr2), anti-N-methyl-D-aspartate receptor (NMDAR), anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), anti- γ -aminobutyric acid receptor (GABA), and glycine receptor. For the purpose

of this review, cases of clinical studies of autoantibody-associated encephalitis were collected, the key points regarding the pathogenesis were summarized, the clinical manifestation was discussed, and all this information was organized as this review in order to introduce the relationship between autoantibodies and autoimmune encephalitis. Furthermore, it is hoped that it can effectively direct the development of diagnostic and therapeutic approach in the future.

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Introduction

Autoantibodies have been shown to play a key role in the manifestation of several neuromuscular diseases since 1970. For example, autoantibodies against acetylcholine receptors and voltage-gated calcium channel (VGKC) are involved in myasthenia gravis and Lambert-Eaton syndrome, respectively. Several in vitro and in vivo studies have confirmed pathogenic effects of such antibodies [1]. Studies about autoantibodies have led to the discovery of anti-neuronal antibodies for specific tumors in the serum of patients with typical paraneoplastic neurological disorders. However, these patients are not immunosuppressed.

A recent research has revealed a key relationship between certain anti-neuronal antibodies and neuronal surface proteins, both in case of adult as well as pediatric patients, which has given rise to the concept of autoimmune encephalitic [2]. Autoimmune encephalitis is caused by autoantibodies against neuronal surface antigens and is treated with different modes of immunotherapies. Patients of autoimmune encephalitis are generally immunosuppressed without any association with tumors. Although the effect of immunotherapeutic treatment might be slower than the effect of peripheral antibody-mediated disease, it can significantly improve the patients' condition over a period. The autoantibodies produced by the immune system bind to the neuronal surface antigens, whose neurological manifestations are called neuronal surface antibody syndrome (NSAS). These antibodies, which act on the surface of neurons, mainly include VGKC antibodies, antibodies against glutamate receptors and GABA receptors. Anti-VGKC antibodies comprise of specific antibodies against different subunits of VGKC or associated protein complexes, like antibodies against leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein 2 (CASPR 2).

Neuronal surface antibody-mediated autoimmune encephalitis is clinically rare. Recent studies have resulted in the gradual recognition and treatment of the disease, potentially leading to the discovery of more specific antibody-mediated immunotherapy in the future. This article reviews the pathogenesis, clinical manifestations, therapeutic approach, and other aspects of antibody-mediated autoimmune encephalitis in order to spread awareness about this disease.

VGKC-Mediated Autoimmune Encephalitis

VGKC complexes are widespread in the nervous system, particularly in peripheral motor nerves. Langfag's knots at sensory nerve endings and synapses are mainly caused by and in close proximity to Kv1 subunits on the surface of neuronal cell membranes [3]. VGKCs open after each action potential and result in the repolarization of the cell membrane. Thus, VGKCs play an important role in the regulation of the electrical activity in the nervous system.

VGKC antibodies were first described in cases of neuromyotonia and Isaac's syndrome. They are characterized by irritated peripheral nerves, presenting as spontaneous fascicular fasciculation, ankylosis, muscular atrophy, and spontaneous potential bursts at high-frequency

stimulation viewed on EMG. This is attributed to the repetitive and spontaneous electrical activity of muscles, caused by motor hyperactivity. VGKC antibodies are found in approximately 40% of neuromyotonia patients and more commonly in patients with Morvan's syndrome and non-paraneoplastic limbic encephalitis [4].

VGKC antibodies are mainly associated with limbic encephalitis. Marginal encephalitis mainly manifests as acute or subacute memory disorders, epilepsy, mental behavioral changes, sleep disorders, hyponatremia, and a certain level of medial temporal lobe and/or hippocampus abnormalities [5, 6]. VGKC antibodies do not bind directly to VGKCs but to specific subunits of VGKCs and associated protein complexes like LGI1, Caspr2 and, Conjugate 2 [7].

Anti-LGI1 Encephalitis

LGI1 is a secreted protein that binds to various proteins of the metalloproteinase family, mainly in the hippocampus and the temporal cortex. It links a disintegrin and metalloprotease protein 23 (ADAM23) to the presynaptic membrane, and a disintegrin and metalloprotease protein 22 (ADAM22) to the postsynaptic membrane, thus playing an important role in the inhibitory signaling between the presynaptic membrane and postsynaptic membrane. The LGI1 antibody minimizes the interaction between the LGI1-associated metalloproteases and thus reduces postsynaptic AMPAR aggregation [8]. Gene disruption of the human-encoded LGI1 protein can lead to autosomal dominant temporal lobe epilepsy [9]. In a study by Fukata et al. [10], 3-week-old mice with knocked-out LGI1 gene died due to severe epilepsy, confirming that LGI1 plays an important role in synaptic signaling. The average age of LGI1-mediated encephalitis onset is 60 years, and the male-to-female ratio is 2:1 [7, 11]. Most patients manifest marginal lobe encephalitis, which is characterized by subacute onset of memory disorders, behavioral changes, disorientation, and epilepsy, including various types of partial and/or total tonic-clonic seizures. LGI1 limbic encephalitis (LGI1-LE) is very specific and is characterized by faciobrachial dystonic seizure (FBDS), also known as ankylosing seizure, in more than 50% of the patients. FBDS is a short (less than 3 s) and high-frequency upper extremity twitch that can also affect the ipsilateral face and lower extremities. As electroencephalogram can detect changes in only a small number of patients with FBDS during the period of attack, its detection and diagnosis by clinicians is very limited. FBDS generally manifests before cognitive decline and early adoptive immunotherapy has the scope to improve the prognosis

of limbic encephalitis [12]. Approximately 60% of LGI1-LE patients also have hyponatremia. In approximately two-thirds of LGI1-LE patients [7, 11], brain MRI shows a strong signal in the middle temporal lobe (T2). Patients with FBDS may present abnormal changes in the basal ganglia [13]. In addition, the cerebrospinal fluid (CSF) may demonstrate minor changes, such as a slightly increased cell count and/or protein expression. The diagnosis of LGI1-LE is based on the detection of LGI1 antibodies in the serum and CSF. However, serum is used more often as it is more sensitive to the detection [14]. Although no randomized controlled studies have been conducted regarding the effectiveness of immunotherapy to treat LGI1-LE, it has been used successfully to treat a few patients. Immunotherapy, including intravenous or oral glucocorticoids, intravenous immunoglobulin, or a combination of both, has been shown to significantly improve the symptoms [7, 11]. The improvement in epilepsy, especially FBDS, progresses rapidly, whereas cognitive function improves gradually.

Anti-CASPR2 Encephalitis

CASPR2 is a membrane protein widely expressed in the central and peripheral nervous system. Mutations in the CASPR2 gene can lead to partial epilepsy, schizophrenia as well as other neurological dysfunctions [15]. Anti-CASPR2 antibodies can affect multiple sites of the central and peripheral nervous system [16]. Although LGI1-LE is more prevalent, the incidence of cases with anti-CASPR2 encephalitis is increasing constantly. In this case, the age of onset is 60 years, and it is prevalent in male patients (about 80–90% male patients) [7, 16]. The common symptoms involving the central nervous system are cognitive decline and seizures. Some cerebellar symptoms, like dizziness and ataxia, have also been reported [7, 16]. Peripheral nerve hyper-excitability can cause muscle tremors and cramps. These symptoms, if accompanied with autonomic dysfunction and insomnia, are classified as Morvan's syndrome. This syndrome is closely related to CASPR2 antibody, although antibody-negative cases have also been reported. CASPR2 antibody-associated encephalitis is often misdiagnosed as Creutzfeldt-Jakob disease [17, 18]. The reason for this is still unclear. It is unclear whether the CASPR2 antibody test in these patients produces false-positive results or if the antibody is unrelated to the disease. The tumor detection rate of patients with CASPR2 antibody-associated encephalitis ranged between 0 and 32% [7, 16, 19]. Among the different types of tumors, thymoma was the most common type detected, followed by myasthenia gravis. Other types

like lung and endometrial tumors have also been reported in a significant number of patients [7]. In order to achieve improvement of the symptoms of the nervous system, it is essential to treat tumors effectively. Immunotherapy, the most effective therapeutic approach for treating autoimmune encephalitis, was also effective in patients who did not have any tumorigenesis [7, 16]. First-line therapies include glucocorticoids, intravenous immunoglobulins, and plasmapheresis. In order to improve prognosis, treatment should be initiated immediately after diagnosis [20]. CASPR2 antibody-mediated encephalitis also has a significant chance of relapsing, similar to LGI1-LE.

Anti-NMDAR Encephalitis

Anti-NMDAR encephalitis is a special clinical manifestation of encephalitis, which primarily affects children. It is characterized by neuropsychiatric symptoms and dyskinesias. It is also sometimes described as immune-mediated dance encephalopathy syndrome, coma with movement disorders, and coma encephalitis [21, 22]. Autoantibodies against NMDAR can be detected in the serum or CSF of patients and they primarily bind to the NR1 subunit of the extracellular epitope of NMDAR [22]. Several studies have worked towards clarifying the clinical manifestations of this disease. Some patients with anti-NMDAR antibodies have significant or isolated psychotic symptoms, dystonia, and epilepsy, without typical multi-stage clinical manifestations that may indicate incomplete resistance to NMDAR encephalitis [23]. In fact, it is the most common etiology of non-infectious encephalitis (except for acute disseminated encephalomyelitis in children). A retrospective study showed that up to 1% of patients previously treated under intensive care were found to have encephalitis of unknown etiology and subsequently confirmed as having anti-NMDAR encephalitis [24]. Anti-NMDAR encephalitis manifests in both men and women. In men, it is associated with testicular teratomas [25]. Other malignancies, including mediastinum and testicular teratoma, Hodgkin's lymphoma, small cell lung cancer, and neuroblastoma, are also associated with anti-NMDAR encephalitis. The tumorigenic association of anti-NMDAR encephalitis is most prominent in children, especially infants [26, 27]. Up to 80% of patients were ultimately diagnosed with non-paraneoplastic anti-NMDAR encephalitis [22]. Studies have shown that although patients had no significant CSF abnormalities, they still manifested varying degrees of increased CSF lymphocytes, protein content, and oligoclonal bands [28].

The MRI results of patients can be normal or display high FLAIR signal in the medial temporal lobe or punctate high signal in the frontal or parietal cortex. Other studies have shown that PET demonstrates acute cortical hypermetabolism and decreased metabolism, which may be associated with subacute anti-NMDAR encephalitis [29].

Autoantibodies against NMDARs lead to a reversible decrease in the local surface density of NMDAR at synapses through various mechanisms, including antibody-mediated overlay and internalization of the NMDAR at the neuronal surface [30, 31]. This mechanism is specific to NMDAR, and it does not affect other glutamate receptors, synaptic proteins, or cell survival, since hippocampi and amygdala express high concentrations of NMDAR, and thus may be more vulnerable to anti-NMDAR autoantibodies (destroying the blood-brain barrier) [32].

The prognosis of anti-NMDAR encephalitis has been studied in many patients who have recovered or have mild sequelae [23]. However, despite the success of immunotherapy in case of many patients and the reversibility of NMDAR disruption, 45% of patients still do not recover completely, 30% patients have a poor prognosis, and approximately 4% patients succumb to the disease [23, 27]. Tumor resections and immunotherapy are not mandatory for rehabilitation, as some patients recover even without receiving any immunotherapy. However, the expense of this natural cure is delay in hospitalization and associated serious complications that may arise due to the delay in hospitalization and lack of proper regular care. After the identification of the patient's symptoms and antibodies, targeted immunotherapy should be initiated as soon as possible [33]. Approximately 48% of patients without tumors had substantial improvements after first-line immunotherapy compared with 80% of patients with tumors. Paraneoplastic group, ovariectomy, and clinical improvement time were found to be significantly correlated. A comprehensive cognitive assessment found that there is a significant persistence of cognitive impairment in many patients, particularly in executive function and memory functional areas, where NMDAR plays a central role [34]. Earlier treatment is associated with more significant improvement in cognitive function. These results suggested that the outcome of treatment of autoimmune encephalitis (e.g., NMDAR encephalitis) may be less optimistic, and that the long-term morbidity of these diseases may be underestimated.

Early onset of symptoms, early diagnosis, and immunotherapy reduced the level of anti-NMDAR antibodies, minimized the likelihood of recurrence, and improved the prognosis of neurological symptoms [22, 35]. The re-

lapse rate in this case was in the range of 12–25% and the risk factors included the lack of immunotherapy as the first-line treatment and lack of tumor diagnosis [20, 23, 36]. However, recurrence indicated that tumor activity can also occur alone, in some cases even 15 years after onset [28, 36]. Tumor diagnosis can also be considerably delayed (by up to 7 years) after the manifestation of early clinical symptoms of encephalitis [33].

Anti-AMPA Encephalitis

AMPA is a subtype of glutamate receptors, which is mainly found in the excitatory synapses of the central nervous system. Anti-AMPA autoantibody binds to the GluR1 and GluR2 subunits of the AMPA extracellular domain and can lead to specific manifestations of limbic encephalitis. Some studies suggest that anti-AMPA encephalitis is more common in women than in men and can be associated with cancer [37, 38]. Although tumor treatment and immunotherapy are effective, the possibility of relapse still exists. A study using 22 patients showed that the clinical manifestations of limbic encephalitis included psychiatric symptoms and multifocal encephalopathy [39]. First-line drug therapy included hormones and intravenous immunoglobulin. In addition, tumor resection can also completely or partially relieve the symptoms. Although there is some possibility of relapse, continued treatment with rituximab or cyclophosphamide may successfully prevent relapse.

Anti-GABA Encephalitis

GABA is widespread in presynaptic and postsynaptic sites of the CNS. Mutations in the GABA gene can lead to epilepsy and cognitive dysfunction. Antibodies against the B1 subunit of GABA can also be detected in patients with limbic encephalitis. Although ataxia is rare in these patients, approximately 50% of the patients also suffer from small cell lung cancer [40]. Immunotherapy combined with chemotherapy or tumor resection can quickly alleviate the symptoms, and in some cases, this combination therapeutic approach can even cure the patient. However, patients who do not receive immunotherapy had a poor prognosis and most of them died within months of developing neurological symptoms. Some patients, even with continued immunotherapy, demonstrate a relatively poor prognosis. It is often associated with tumor progression or with antibodies against intra-

Table 1. Comparison with different NSAS style clinical characteristic

Antibody	NMDAR [20, 23, 28, 36]	LGI1 [7, 11]	Caspr2 [7, 16]	AMPA [37, 39, 48]	GABAR [40–43]	Glutamate R [45, 46, 49]
Age	More common in age 2 to 40 years	30–80 years, average about 60 years	45–80 years, average about 60 years	23–81 years, average about 62 years	25–75 years, average about 50 years	5–69 years, average about 49 years
Gender	80% is female	65% is male	85% is male	64% is female	Female:male = 1:1	45% is male
Neurological manifestations	Mental and behavioral abnormalities, epilepsy, aphasia, dyskinesia, central hypoventilation, autonomic nerve abnormalities	Facial arm dystonia, seizures, memory disorders, sleep disorders	Isaac's syndrome, Morvan's syndrome, sleep disorders	Edge encephalitis, psychiatric symptoms	Edge encephalitis, psychiatric symptoms, epilepsy	Progressive encephalomyelitis with stiff man syndrome
Cerebrospinal fluid	90% is abnormal as lymphocytosis, oligoclonal band and elevated protein	40% abnormal, nonspecific	25% is abnormal mildly	90% is abnormal, oligoclonal band	80–90% is abnormal, oligoclonal band	Can be normal or can elevate lymphocyte, protein, oligoclonal bands
Medical imaging (MR)	50% is abnormal, T2 or FLAIR is high signal in middle temporal lobe and focal cortical	85% of patients' T2 have high signal in middle temporal lobe	40% is abnormal, FLAIR is high signal in middle temporal lobe	90% is abnormal, FLAIR is high signal in middle temporal lobe	65% FLAIR is high signal in temporal lobe	Mostly normal
Tumor	Including ovarian teratoma, thymoma, mediastinal tumor, Hodgkin lymphoma; ovarian teratoma is the most common; tumors are rare in children and males	Uncommon	20–40% produce thymoma	70% patients have tumors, mainly include small cell lung cancer, breast cancer, and thymoma	45–60% patients have tumors, mostly small cell lung cancer	Uncommon
Other	12–25% relapse	Few relapses, sometimes hyponatremia may exist	None	50–60% relapse	None	None

cellular antibodies or antigens that appear to be involved in the pathogenesis of T cell-mediated cytotoxicity during disease progression [41]. In another study by Lancaster et al. [40] on 15 patients with antibody-positive marginal encephalitis, 7 patients also suffered from small cell lung cancer [42]. Unlike paraneoplastic encephalitis, these patients were sensitive to immunotherapy. Out of these patients, 3 presented other antibodies and different clinical manifestations.

Recently, a new autoantibody directed against the alpha subunit of GABAR has been discovered. Such antibodies act on the $\alpha 1/\beta 3$ subunit of the receptor. Petit-Pedrol et al. [43] reported cases of 18 patients, in which the serum and CSF antibody titers were high for 6 patients who had typical clinical symptoms. In the remaining 12 patients with low antibody titers, the antibodies could only be detected in serum along with other antibodies. Out of the 6 patients in which the antibodies were detected in CSF, only 1 patient was cured with antiepileptic drugs, but long-term use was required to avoid recur-

rence. Three patients out of the other 5 patients who received different treatments (hormonal therapy alone or in combination with intravenous immunoglobulin, plasma exchange, cyclophosphamide, or rituximab) recovered and the other 2 patients died of sepsis.

Pettingill et al. [44] reported a study of 40 patients treated with immunosuppressive agents. They responded to GABA receptor, a subunit antibody, which bound to the $\alpha 1$ and $\gamma 2$ subunits of the receptors. Only 1 out of these 40 patients exhibited significant improvement in psychiatric symptoms and cognitive dysfunction as the antibody titers declined.

Anti-Glutamate Receptor Encephalitis

These antibodies bind to the $\alpha 1$ subunit of glutamate receptors. Anti-glutamate receptor antibody-positive encephalitis patients have been considered variants associated with progressive encephalomyelitis, stiffness, myoc-

lonus, and other symptoms of stiff-person syndrome. However, these diseases are characterized by stiff stimulus-sensitive spasms, myoclonus, autonomic dysfunction, and brainstem lesions [45]. In one case study, patients treated with immunotherapy demonstrated significant improvement in symptoms, the improvement in symptoms continued and even completely disappeared in some cases [45]. Although many forms of treatments are available, the classic treatment is methylprednisolone impact therapy or plasma exchange with intravenous immunoglobulin, followed by oral prednisone to maintain treatment. However, out of 45 patients, 6 patients recurred and required long-term use of immunosuppressive agents, such as mycophenolate mofetil, azathioprine, or cyclophosphamide. Studies have found that glutamate receptor autoantibodies are detected in patients with isolated optic neuritis, and focal epilepsy is more common in adult patients [46, 47]. However, in this study, the persistence of antibodies was also detected in a number of patients in the control group and the antibody titers were unrelated to clinical manifestations and drug therapy. In this case, the role of autoantibodies against glutamate receptors is not associated with significant clinical benefits.

In summary, the concrete characteristics of NSAS are listed in Table 1.

Zuliani et al. [30] have proposed clinical diagnostic criteria for NSAS patients. They recommended that NSAS should be diagnosed when the patient presents with acute- or subacute-onset symptoms, CSF abnormalities, and imaging or histopathology supporting inflammatory changes and that other causes of infection, metabolism, and intoxication should be excluded. The diagnostic criteria included a history of other autoimmune diseases and prodromal infections. The diagnostic criteria described above are combined with the patient's treatment to determine a definitive or probable diagnosis. However, no definitive treatment guide is currently available for specific antibody-mediated encephalitis. The typical treatment is corticosteroid shock therapy followed by a high dose of oral prednisone and intravenous immunoglobulin and plasma exchange as first-line therapy [30]. Ramanathan et al. [50] recommended concurrent treatment: methylprednisolone therapy for 3–5 days (30 mg/kg/day to 1 g/day) followed by a high dose of oral prednisone (1–2 mg/kg/day) and intravenous immunoglobulin for 2–5 days (2 g/kg). If this treatment does not show any effect within 1–2 weeks, then plasmapheresis for 3 to 5 times may be considered, or second-line drugs, such as cyclophosphamide or rituximab, may be initiated. No information is available as to whether rituximab

or cyclophosphamide is more effective [51]. The best treatment is assessed based on the patient's clinical status, not just the antibody titer, which may not be directly related to clinical progression.

Understanding the etiology and pathogenesis of a disease is crucial to its treatment. It mainly mediates central nervous system damage through humoral or cellular immune response. Among them, neuronal surface protein antibodies usually have definite pathogenicity. Such antibodies can lead to a reversible decrease in the neuronal surface receptors, but do not cause neuronal necrosis. Tumor and prodromal infection are often the cause of this disease, for example, the incidence of ovarian teratoma is higher in young women with NMDAR encephalitis, small cell lung cancer in patients with edge encephalitis associated with anti-GABABR antibody, herpes simplex encephalitis can lead to the development of anti-NMDAR encephalitis. Different central nervous system autoimmune diseases are likely to have different antibody-mediated pathogenesis. In a histopathological study, Bien et al. [52] identified a high CD8/CD3 ratio in patients with anti-Hu and anti-Ma2 autoimmune encephalitis and cytotoxic T cell-induced neuronal loss. These were matched to the initial T cell-mediated pathogenesis. By contrast, in patients with VGKC-associated antibodies, studies suggested that complement deposition, which in turn leads to neuronal loss, is the primary pathogenic mechanism. In anti-NMDAR patients, the density of inflammatory cells is low, and there is insufficient evidence that suggests the pathogenic mechanism is an antibody- or complement-mediated cell injury. However, in chronic patients, studies [51] suggested that there is inflammatory infiltration of B and plasma cells in anti-NMDAR encephalitis.

Whether the long-term use of immunomodulatory drugs, such as mycophenolate mofetil or azathioprine, could prevent relapse remains unclear to date. Tumor-related examinations should be performed during the initial onset and regular follow-up, along with a full-body PET examination. Pelvic MRI should also be performed in patients with anti-NMDAR encephalitis [23, 30]. When NSAS is highly suspected, first-line drug treatment should be initiated while excluding infection, antibody testing, and tumor-related tests [30]. Although controversial, most studies [53] suggested that when NSAS is highly suspected, treatment should be given early, even if the antibody is negative, because early treatment may improve the patient's prognosis.

Undoubtedly, more and more patients are diagnosed with NSAS based on clinical manifestations, antibody-

related tests, histopathological tests, and immunotherapy. In this paper, different cases of antibody-mediated encephalitis were described in detail to enhance the understanding of this disease and consequently avoid misdiagnosis and missed diagnosis. We believe that once the diagnosis of autoimmune lesions is supported by the patient's medical history and related examinations, immunotherapy should be administered as soon as possible to improve the patient's prognosis even if no relevant antibody test was conducted or if the result was negative [54, 55]. At present, not only the non-found antigens, antibodies, or their pathogenesis, but also the effective treatment plan for antibodies are needed to have a further study.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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Author Contributions

Meiling Wang and Jianmin Li contributed the central idea. Rui Liu and Mingkai Zhang wrote the initial draft of the paper. The remaining authors contributed to refining the ideas, carrying out additional analyses, and finalizing this paper.

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