A critical reflection on our first patient presenting with Anti-N-methyl-D-aspartate receptor encephalitis

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Abstract

One of the best characterized autoimmune encephalitis is the Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, which may occur in the presence of cancer. First- and second-line immunotherapy and oncological investigations are suggested. We present here a case of an 18-year-old female who was our first patient suffering from Anti-NMDAR encephalitis more than 9 years ago. She was satisfactorily treated with intravenous immunoglobulins and high dose steroid therapy. After more than one year the patient had a relapse. First-line immunotherapy was repeated; however, a complete recovery was achieved only after plasmapheresis. Afterwards, she continued maintenance immunotherapy with steroids for two years and with Azathioprine for about five years associated to regular oncological assessment. In the last years our therapeutical approach of Anti-NMDAR-encephalitis has significantly changed. Nevertheless, established treatment guidelines are still missing and the role of long-term maintenance immunotherapy is largely unexplored. In addition, oncological revaluation might be indicated in selected patients.

Introduction

Encephalitis is an inflammatory condition of the brain with many different etiologies; several are immune mediated.[1] The best characterized autoimmune encephalitis (AE) is the Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, with antibodies against neuronal cell surface/synaptic proteins. Anti-NMDAR encephalitis may occur in the presence or absence of cancer. Where a tumor association exists, it can be considered as a paraneoplastic encephalitis syndrome. In 2005, Anti-NMDAR encephalitis was described for the first time,[2] although the target antigen was identified only some years later.[3] Since then, hundreds of papers about Anti-NMDAR encephalitis have been published, increasing our knowledge of clinical characteristics, diagnostic findings, therapeutical options and pathogenic mechanism.

Our first patient presenting with Anti-NMDAR encephalitis occurred in April 2010. The patient's clinical presentation and multistage progression were nearly identical with previous case descriptions in literature.[4-6] Thus, once an infectious etiology had been ruled out, the diagnostic hypothesis of an autoimmune mediated encephalitis was becoming predominant.

Case Report

An 18-year-old female patient was admitted to our hospital due to a first-time generalized seizure. Neurological examination was normal, and from her medical history only a minor thalassemia was reported. Four days before hospital admission she had suffered from low-grade fever and recurrent vomiting. A brain magnetic resonance imaging (MRI) did not show any abnormalities. An electroencephalogram (EEG) demonstrated a well-organized background activity and only rarely recurrent theta-delta slowing involving mainly the left fronto-temporal leads. A study of the cerebrospinal fluid (CSF) revealed mild pleocytosis with a predominance of lymphocytes (10/mmc) and a slightly increased protein concentration (61 mg/dL). During the following days the patient's clinical presentation demonstrated a progressive deterioration: she developed first an expressive, then a global aphasia, combined with psychotic symptoms (visual hallucinations and paranoid thoughts) and abulia. Many laboratory investigations in serum and CSF were performed including the search for antibodies directed against neuronal cell surface/synaptic proteins, with antibodies against the NMDAR in the patient's CSF and serum demonstrating a positive result. In order to exclude a paraneoplastic-mediated encephalopathic process, oncological assessment was subsequently performed including abdomen and pelvis MRI whereby a teratoma was ruled out.

Six days after admission, the patient started immunotherapy characterized initially by high dose intravenous (iv) steroid therapy (methylprednisolone 1 g/day for 5 days), followed by slowly tapering and then by oral maintenance steroid treatment (prednisone 50 mg/day). In parallel, the patient received iv immunoglobulins (IVIg) (18 g/day for 5 days). During the first month of immunotherapy the patient developed decreased consciousness, progressing to a catatonic-like state with recurrent orofacial dyskinesias and signs of autonomic instability (paroxysmal sinus tachycardia with heart rates greater than 200 beats/min and hypoventilation). This clinical deterioration required admission to the intensive care unit. Repeated brain MRIs (on day 8, 14 and 28) did not demonstrate any significant changes in signal. Extensive EEG monitoring revealed a progressive, disorganized background activity with diffuse slowing, but no epileptic discharges. After six weeks the patient begun to show a slowly but steady improvement of

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consciousness and cognitive functions. Ten weeks later she still presented with significant cognitive deficits, especially in speech production and syntax comprehension, and bizarre behavior. After four weeks in a cognitive rehabilitation center the patient still showed signs of frontal-lobe dysfunction. A further four and a half months later she could finally go back to school, however, she had significant learning difficulties which required repeating a school year. She underwent periodically neurological and oncological assessments in our hospital, and continued oral maintenance steroid therapy with prednisone which was slowly tapered and finally stopped in April 2011.

In September 2011 the patient had a relapse of the Anti-NMDAR encephalitis which was characterized by psychotic symptoms such as behavioral abnormalities (self-induced vomiting and paranoid and persecutory ideas) and cognitive problems (dysfunction of attention and memory loss). The search for antibodies anti-NMDAR in the patient's CSF resulted positive, while brain MRI, EEG and oncological investigations were negative. The patient received again high dose iv steroid therapy and IVIg, however, a complete recovery was obtained only after five procedures of plasmapheresis. The patient was dismissed with daily maintenance steroid therapy (prednisone 50 mg/day) and azathioprine (AZA) (50 mg/twice a day). In order to avoid additional relapses, immunosuppressive therapy with AZA was continued for about five years, while corticoid treatment was stopped in September 2013 due to significant side effects such as a bilateral glaucoma and metabolic changes (obesity and initial osteoporosis).

During all these years the patient underwent regularly radiological investigations in order to rule out a paraneoplastic etiology of her AE. An associated cancer, in particular a teratoma, has never been detected. Antiepileptic treatment was not indicated as the patient had suffered only from an acute symptomatic seizure at the very beginning of the encephalitic syndrome. Today in August 2019, more than nine years later, the patient is doing very well. The previous side effects of prednisone have disappeared completely and the patient's cognitive functions are nearly identical with those before her encephalitis. Looking back, we are very happy about the patient's favorable outcome, however, a critical analysis of our clinical-therapeutical approach in 2010 regarding Anti-NMDAR encephalitis has led to some reflections.

Discussion

The patient had started first-line immunotherapy after six days of admission. She did not receive second-line treatment, even after her relapse. In the last few years, several patients with AE have been seen in our Department of Neurology, and our therapeutical approach has definitively changed. In general, first-line immunotherapy is started earlier (usually already two-three days after hospital admission), still characterized by iv methylprednisolone associated either with IVIg or plasmapheresis. The earlier treatment beginning derives from a better recognition of patients affected by Anti-NMDAR encephalitis or other kinds of AE. This might be mainly a consequence of our personal experience, but also due to the introduction of criteria and guidelines for the clinical diagnosis of AE in 2016.[7] In addition, the testing for antibodies directed against neuronal cell surface/synaptic proteins has become much easier during the last few years, and the results are available in shorter times (the tests were previously performed abroad, taking many weeks).

Regarding the treatment, in most cases, we now proceed usually with second-line immunotherapy, mainly with rituximab, a widely used B-cell-depleting monoclonal antibody, in order to avoid relapses and to guarantee a favorable outcome. In 2010 our treatment behavior was much less aggressive, and drugs such as rituximab were not routinely used in our Department of Neurology as its indication for neurological diseases was off-label. Instead, we applied an alternative approach characterized by steroids, which were progressively tapered, in combination with a chronic immunosuppressive agent, namely with AZA, started after the patient's relapse. Under this treatment our patient did not present any more relapses, maybe also because the immunotherapy was continued for nearly five years. Until today none of our other patients with AE has received such a long-lasting maintenance immune-modulating therapy.

Looking back again to the patient's history, the initial outcome was unsatisfactory as the patient was still suffering from important cognitive deficits. Although the patient's recovery was insufficient, re-administration of first-line treatment or additional immunotherapy were not taken in consideration, probably because in the literature it had been reported that a certain percentage of patients affected with Anti-NMDAR encephalitis had a less favorable outcome, and that cognitive sequelae might be persistent.[5,6,8] In addition, our patient demonstrated a slowly but progressive clinical improvement while performing cognitive rehabilitation. Today, in cases of inadequate response to first treatment given, first-line immunotherapy is repeated or second-line treatment is started if not already administered before.

Thus, our treatment options have become much more aggressive, even if several drugs (*i.e.* rituximab) are still unlicensed for use in neurological disorders. This behavioral change is based on our personal experience and on a number of expert recommendations on immunotherapy for Anti-NMDAR encephalitis or other AE which have been published in the last years.[9-11] Nevertheless, so far there are no established guidelines for treatment of AE, and diverse regimens are currently used, based on the patient's clinical status and the clinician's opinion. Although the expert recommendations are very useful, there remain a lot of open questions. For example, the optimal duration of immunosuppressive treatment has not yet been established. Also, the indication for second-line immunotherapy is not clear: should second-line treatment always be administered or only in severe cases or after relapses? Anti-NMDAR encephalitis is mostly monophasic, and instances of spontaneous recovery without immunotherapy or tumor resection have been reported.[5,6] On the other hand, relapses of AE have been described even after five to ten years[12] and relapses in Anti-NMDAR encephalitis have been reported in 9 to 23 per cent of patients.[13] Indeed, early aggressive therapy is referred to reduce relapse rates,[14] which would be consistent with our personal experience. However, the choice of second-line treatment is not always easy, especially due to possible side-effects and missing licenses. In some patients second-line treatment might be impossible; hereby a long-lasting maintenance immunotherapy could be a therapeutical alternative.

In practice, the therapeutic recommendations focus mainly on first and second-line treatment, on the contrary, the role of maintenance immunotherapy is largely unclear. AZA and mycophenolate mofetil (MMF) are commonly used oral steroid-sparing agents for maintenance therapy in autoimmune neurological disorders.[15] In addition, AZA is amongst the oldest pharmacologic immunosuppressive agents in use today, therefore it is a well-known drug, including its side-effects, that has a reasonable safety profile.[16] Thus, AZA might be useful if following acute treatment of NMDAR encephalitis for sustained remission.[10] On the other hand, as mentioned

previously, Anti-NMDAR encephalitis is mostly monophasic and relapses might be avoided by second-line treatments, thus, this raises the question as to whether a chronic immunosuppressive treatment is really necessary. Nevertheless, it is known that Anti-NMDAR encephalitis, following a Herpes simplex virus encephalitis, might exceptionally become a chronic autoimmune disorder.[17] In these rare cases a long-lasting immunosuppression could be indicated; but then, what is about the risk of viral reactivation? In literature there are only few publications that talk about long-term immune suppression in AE, in particularly with AZA. Nosadini et al. have published an interesting review article regarding MMF, AZA and methotrexate usage in pediatric anti-NMDAR encephalitis.[18] The review shows that AZA has been used only in a minority of cases and mainly after relapses have occurred. In addition, the review demonstrates that the duration of maintenance treatment was highly variable (range 1-48 months), confirming that the role of long-term immunosuppression with oral agents is still unclear regarding AE. To our opinion, oral steroid-sparing immunosuppressants might be useful in very selected patients and for that reason these drugs should be considered in future treatment guidelines for AE.

We have noted one other difference in our clinical behavior analyzing our case from 2010: the patient was performing tumor assessment for almost 5 years (at the beginning twice a year, then once a year). Since today, patients affected with AE are scheduled for regularly neurological visits, however, thorough tumor screening is mostly performed only at the moment of diagnosis. To our knowledge, in literature serial oncological investigations are never reported. However, in patients presenting with NMADR encephalitis or other AE, characterized by severe persistent deficits or relapses, a second tumor search might be indicated, also because it is known from other paraneoplastic syndromes that neurological manifestations occur often prior to symptoms of malignancy.[19]

Conclusions

Looking critically back on the clinical-therapeutical approach to our first patient affected from Anti-NMDAR encephalitis in April 2010, we think that established treatment guidelines for AE are still needed, in order to determine the appropriate therapeutic option and duration of immunotherapy for sustained remission and positive outcome. Interestingly, the role of long-term maintenance therapy is largely unexplored, probably because Anti-NMDAR encephalitis is mostly not a chronic relapsing disease. In highly selected patients, long-lasting immunotherapy might be indicated, as well as an oncological revaluation.

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