Table 1: Contd...

Patient	Sex	Age	Teratoma	Surgery	Glucocorticoids	IVIg	Serum exchange	Rituximab	Anti-virus	Prognosis	Author
34	Female	47	Yes	No	Yes	No	-	-	-	Favorable and no recurrence	Our case
35	Female	17	Yes	Yes	-	Yes	-	-	-	Favorable and no recurrence	Our case

IVIg: Intravenous immunoglobulin; N/A: Not applicable; "-": Not mentioned by author

our investigation, the mean price of an antibody test is about 60 dollars for the reported patients in China.

Treatment

Regarding to the treatment for anti-NMDAR encephalitis, Dalmau *et al.*[18] provided a treatment proposal for this disease in 2011 [Figure 1]. They prefer concurrent intravenous immunoglobulin (IVIg) (0.4 g/kg/day for 5 days) and methylprednisolone (1 g/day for 5 days) to plasma exchange. As for the second-line therapy, they often use rituximab combined with cyclophosphamide in adults. And in children, they often use only one of these drugs – mostly rituximab. In China, anti-NMDAR encephalitis as a new disease, is often confused with viral encephalitis, and is treated with acyclovir or/and virazole. When the diagnosis was uncertain, some doctors gave IVIg as an alternative to the patients who did not respond to anti-viral treatment. Rituximab was seldom used for anti-NMDAR encephalitis patients due to its high cost, and lack of doctor's experience with the drug [Table 1].

Prognosis

Gresa-Arribas *et al.*[41] conducted a 5-year study with 501 patients. Their findings include: (1) 81% of anti-NMDAR encephalitis patients had favorable outcomes from immunotherapy, and factors affecting these outcomes include early diagnosis and nonintensive care unit treatment; (2) risk of recurrence is about 12% within 2 years, of which 67% is less harmful as compared with the first outbreak; (3) normally, the second-line immunotherapy was effective when the first-line therapy had failed.[41] Based on the long-term follow-up, the higher titer of antibody in patients' serum or CSF, worse was the prognosis. There was significant association between CSF antibody titer and the risk of recurrence.[42]

Among the 35 patients with anti-NMDAR encephalitis, one patient was in a continuous stupor-like state, one patient died 4 days after the tumor removal, one patient had an unfavorable prognosis, one patient recurred but improved after IVIg again, and 30 patients (86%) had favorable prognosis without recurrence or sequel [Table 1].

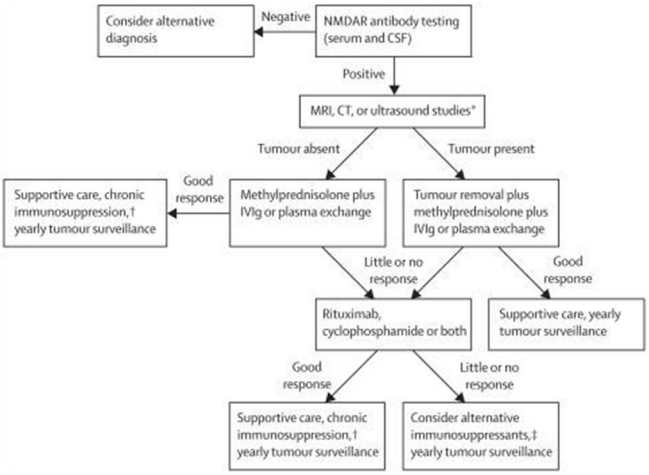

Figure 1: Proposed algorithm for the treatment of anti-N-methyl-D-aspartate receptors encephalitis

OTHER ISSUES RELATED TO ANTI-NMDA RECEPTOR ENCEPHALITIS

Pregnancy

Majority of the patients are females, and the issue of pregnancy is unavoidable. Pregnant patients could deliver a healthy baby if they have no NMDAR antibody in their serum. The curative effect increases significantly after giving birth or after termination of pregnancy.

Synaptic autoimmune encephalopathy

Some types of autoimmune encephalitis, such as anti-NMDAR encephalitis, anti-AMPAR encephalitis, anti-GABABR encephalitis, and anti-LGI1 encephalitis, can be distinguished by the antibodies against the receptors anchored in synapses. There are some common features of these diseases: high incidence in females always associated with tumor, psychiatric disorders, behavioral changes, and refractory seizures. Importantly, these diseases are reversible and curable with immunotherapy and removal of possible tumors, if they are diagnosed at an early stage.

The term of synaptic autoimmune encephalopathy is recommended for labeling these disease, thereby hinting at their favorable prognosis and the necessity for early immunotherapy.

SUMMARY AND FUTURE DIRECTIONS

As compared to patients abroad, Chinese patients normally have a long course of recovery. There are several reasons for this, including inadequate laboratory techniques, absence of standard operating procedures for such type of treatment, insufficient drug treatment, less experience in second-line treatment, and noncompliance of treatment from time to time. This is a big challenge routinely faced by the neurologists in checkups, diagnosis, or treatment.

Viral encephalitis and anti-NMDAR encephalitis have similar clinical symptoms such as headache, fever, mental disorder and seizures, and similar observations in MRI or EEG. It has not been aligned whether glucocorticoid should be used in the early treatment of viral encephalitis. With the incidence of autoimmune encephalopathies rising, we propose that patients with unconfirmed encephalitis could use glucocorticoid once they have a CSF puncture, and IVIg can also be administered.

B-lymphocyte depletion therapy mediated by anti-CD20 monoclonal antibody has been a brilliant breakthrough in the treatment of various antibody-related autoimmune diseases, such as anti-NMDAR encephalitis, rheumatoid arthritis, *etc*. It is important to investigate the possibility of applying this therapy to other higher-incidence neural autoimmune diseases, such as ophthalmoneuromyelitis. The vista is optimistic.

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