A survey on pediatric anti-N-methyl-D-aspartate-receptor encephalitis treatment strategies in China

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To the Editor: Currently, there is no standardized treatment protocol for the pediatric anti-*N*-methyl-D-aspartate receptor (NMDAR). There are two surveys by Kahn *et al*[1] and Bartolini *et al*[2] that aimed at determining the treatment strategies that are used for pediatric NMDAR encephalitis in other parts of the world rather than China. Bartolini *et al*[2] performed a worldwide survey involving 199 participants: 61 adult neurologists, 86 pediatric neurologists, and 52 pediatric rheumatologists. Their survey investigated the differences in anti-NMDAR encephalitis treatment strategies, according to medical specialty, years in practice, and geographical location.[2] The survey of Kahn *et al*[1] involved 151 pediatric neurologists and focused on identifying the indications for the initiation of immunotherapy, type of the used immunotherapy, length of the first-line immunotherapy, time for the initiation of the second-line immunotherapy, and the preferable options for the second-line immunotherapy. Additionally, they investigated the indications and time for adding a disease-modifying therapy, and how long should patients continue with the immunotherapy once returned to their neurologic baseline.[1] Both surveys did not sufficiently focus on identifying the utility of the modified Rankin Scale (mRS), dosages and duration of the treatments (including the duration of oral prednisone), the utility of Cluster of Differentiation 19 positive ($CD19^+$) B cells in adjusting the dosages of rituximab, the necessity of long-term immunosuppressive treatment (for relapse prevention), and the indications for stopping the immunotherapy.

To support the step toward the establishment of a standardized treatment protocol for pediatric anti-NMDAR encephalitis, we performed a large survey in China, in which the responders were mainly pediatric neurologists. This survey evaluated several aspects of pediatric anti-NMDAR encephalitis treatment strategies, including the mRS score utility, the first-line treatment strategies that are being used (dosages and durations), the duration of oral prednisone, the interval between the first- and second-line immunotherapy, the rituximab prescription strategies, the necessity of long-term immunosuppressive treatment, and the indications for stopping immunotherapy.

A total of 200 senior pediatric neurologists, from 125 hospitals, responded to almost all 30 questions. Supplementary Table 1, http://links.lww.com/CM9/A421 summarizes all the questions and responses.

Most respondents were chief neurologists, who, in the majority, diagnosed 1 to 9 cases per year. A combination of methylprednisolone pulse therapy and intravenous immunoglobulin (IVIG) was more prescribed than plasma exchange, which was similar to the other surveys' prescriptions.[1,2] However, adult neurologists performed more plasma exchange in the Bartolini *et al* survey.[2] The plasma exchange might not be preferred for children as it is more invasive and, consequently, may be held as an upfront reserve for most severe cases or older children.

According to most responders, the duration for the prescription of methylprednisolone pulse therapy ranged from >3 to ≤ 5 days. Furthermore, one-third of respondents prescribed a high dose of oral prednisolone for the patients who opted in after intravenous methylprednisolone. The necessity and clear timing for prednisolone tapering remain elusive. Most of the respondents did not use the mRS score to decide whether to start the methylprednisolone pulse therapy. According to the survey of Kahn *et al*,[1] most respondents initiated immunotherapy based on clinical manifestations rather than serological results. The duration of the first-line immunotherapy (including oral prednisolone tapering) ranged from >3 to ≤ 6 months according to many respondents. The survey by Kahn *et al*[1] revealed that most

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Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001308

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Chinese Medical Journal 2021;134(12)

Received: 03-09-2020 **Edited by:** Peng Lyu.

pediatric neurologists prescribed first-line agents for 6 months, while that of Bartolini *et al*[2] did not investigate that aspect.

Nevertheless, further studies are needed to determine the precise duration of the first-line immunotherapy and its influence on the relapse rate and overall prognosis. There was a high chance of repeating the first-line immunotherapy when a patient refused the second-line treatment. According to the survey of Bartolini *et al*,[2] pediatric neurologists were more likely to repeat the first-line immunotherapy when compared with adult neurologists and pediatric rheumatologists. Noteworthy, 12% of pediatricians, who participated in this survey, indicated that rituximab can be incorporated in the first-line immunotherapy.[2]

In our survey, the second-line immunotherapy was more prescribed after the first-line tier failure, and the most common option was rituximab (according to more than three-quarters of the respondents). Approximately 50% of the clinicians indicated that the interval between the prescription of first- and second-line immunotherapy ranges from >14 to ≤28 days. On the contrary, the Bartolini *et al*[2] survey revealed that most respondents, who prescribed second-line agents, did so in ≤2 weeks. The survey of Kahn *et al*[1] showed that most respondents prescribed second-line drugs 1 to 2 months after the failure of the first-line immunotherapy. The early first-line treatment has been reported to associate with better outcomes and fewer relapses.[4] Therefore, we speculated that an early introduction of second-line immunotherapy might be useful too. However, the precise timing remained a challenge.

Most respondents prescribed second-line immunotherapy based on the mRS score and following the completion of the first line tier, with the majority considering an mRS of three as the cut-off value. In this survey, rituximab was more used, followed by cyclophosphamide. Similarly, the largest available retrospective cohort study showed the utility of rituximab as a second-line therapy that was associated with better outcomes and a reduced relapse risk.[4] Most respondents prescribed a regular dose of rituximab rather than its adjustment based on the levels of $CD19^+$ B cells. The monitoring of $CD19^+$ B cell counts can assist clinicians in adjusting rituximab dosages that are associated with several side effects, such as infection, anemia, and thrombocytopenia.[3] For the survey of Bartolini *et al*,[2] fewer pediatric neurologists have choosen rituximab alone as second-line immunotherapy when compared with adult neurologists and pediatric rheumatologists. Instead, the preferable second-line treatment was the combination of rituximab and cyclophosphamide.[2] Besides, most US physicians were more likely to repeat the first-line immunotherapy, by prescribing rituximab or cyclophosphamide alone, compared with physicians in other countries.[2] On the other hand, physicians from other countries, excluding China, were more likely to prescribe a combination of rituximab and cyclophosphamide as well as antimetabolite.[2]

More than 50% of our respondents indicated that long-term immunosuppressive treatment was not a routine treatment. In fact, the commonest prescribed drugs were mycophenolate mofetil, and followed by azathioprine. According to the 29% of the respondents, the prescription duration ranged from >6 to ≤12 months. The survey of Bartolini *et al*,[2] indicated that pediatric neurologists prescribe less long-term immunosuppressive treatment (azathioprine or mycophenolate mofetil) compared with adult neurologists. Conversely, some studies encouraged the utilization of long-term immunosuppressive therapy after the acute phase for a better recovery or relapse prevention.[4]

The indications for stopping immunotherapy included the improvement of the clinical manifestations, followed by cerebrospinal fluid/serum anti-NMDAR antibodies, brain magnetic resonance imaging, mRS scores, and electroencephalogram.

Our survey has some limitations as it is exclusively based on China; thus, prone to bias. It is worth noting that our sample may not represent the total population of pediatric neurologists in China. The survey questions were open to personal understanding and could have been perplexing or ambiguous, depending on each respondent's practice approaches. For the doctors without access to second-line immunotherapies, we did not inquire about the other prescribed options after treatments' failure with the first-line agents.

This survey provides a current update on the treatment strategies for pediatric anti-NMDAR encephalitis in China. In conjunction with two previous surveys, we suggest that the zones of the agreement to be used as a step toward the establishment of standardized treatment guidelines and research protocols should focus on clinical trials. The zones of the agreement include the utilization of methylprednisolone pulse therapy and/or IVIG as the first-line treatment and rituximab as the second-line option. The precise duration of the first-line immunotherapy, the duration of oral prednisolone tapering, the interval between the first- and second-line immunotherapy, and the necessity of long-term immunosuppressive therapy require further investigation. The utility of monitoring $CD19^+$ B cell counts in adjusting rituximab dosage needs to be emphasized.

Conflicts of interest

None.

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How to cite this article: Cao XS, Kessi M, Ji TY, Jiang YW, Yin F, Peng J. A survey on pediatric anti-N-methyl-D-aspartate-receptor encephalitis treatment strategies in China. Chin Med J 2021;134:1498–1499. doi: 10.1097/CM9.0000000000001308