



# The Chinese experience with anti-NMDAR encephalitis

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Anti-NMDA receptor (NMDAR) encephalitis is a severe autoimmune neuropsychiatric disorder characterized by the presence in CSF of anti-NMDAR autoantibodies of the IgG subtype (1-3). It is a recently described disease since the first descriptions date from 2005 (4). Since then, several hundred cases have been reported around the world, and, although the clinical and epidemiological presentation is globally consistent regardless of the population studied (i.e., severe neuropsychiatric symptoms usually affecting children and young adults with a female prevalence and often a good response to treatment), there are differences in their clinical characteristics between ethnicities and countries (5-9). This could suggest variable immunopathological mechanisms possibly influenced by the genetic background or by different environmental factors.

This is the reason why the recent publication by the Peking Union Medical College Hospital of the historical Chinese cohort of 220 anti-NMDAR encephalitis patients diagnosed between 2011 and 2017 in China is of primary importance (10). Indeed, to date, available data regarding the clinical characteristics and long-term prognosis of Chinese anti-NMDAR patients come from only a limited number of reports of small sample size (11-14), and in the largest international cohort published (577 patients from 35 countries), only 8 Chinese patients were included (5). This precluded any conclusion as to the particular characteristics of the disease in this population which is now made possible by comparison with reported cohorts of comparable size,

for instance the French cohort (15-18) and the international benchmark (5).

In terms of clinical presentation, not surprisingly, neuropsychiatric symptoms are largely dominated, here as elsewhere, by behavioral and psychotic disorders and seizures [developed by respectively 82% and 81% of the Chinese patients, and for comparison by 81% and 78% of the French cases (16)]. The first difference observed is epidemiological: effectively if the classic median age of 21 years is the same among reported series, the large female predominance [around 80% (5,18)], is less marked here (65%). This higher proportion of male cases probably accounts for another feature of Chinese patients who less frequently present an associated neoplasm. Knowing that the vast majority of the tumors associated with anti-NMDAR encephalitis are ovarian teratomas, it is quite logical that a smaller proportion of Chinese patients (19.5%) present an underlying neoplasm, compared to the 38% reported, for example, in the international reference study (5). However, this frequency of paraneoplastic cases is comparable to that described in the French cohort [25%, (18)] and half of that reported among the Asian group in the international study (44%) which mainly included Japanese and Korean patients (5). This feature may suggest different immunopathological mechanisms at the origin of the immunization against the NMDA receptor which remain to be identified. As the authors suggest, in tumor-negative patients, herpes

simplex virus (HSV) infection could be the possible trigger that can be underdiagnosed for financial reasons, as most of the patients received empirical treatment without a definite diagnosis of HSV encephalitis which requires PCR testing. Because paraneoplastic cases seem relatively rare, a systematic search for viral triggers in this population could be very interesting.

The most astonishing characteristic in this large cohort is certainly the very largely favorable outcome of Chinese patients at 12 months, since more than 92% of them reach a satisfactory functional score [modified Rankin Scale (mRS) score <2], whereas such a good outcome is obtained in only 78% of the international patients at 24 months (5) and 82% of the French patients at 12 months (15,16). This better short-term outcome is probably partly related to the rapid management of the diagnosis by this national referral center since the authors report an impressive median 2 weeks from onset to diagnosis and concomitant initiation of treatment. Another explanation for this favorable outcome could be a lower clinical severity of the disease; only 133/220 (60%) of patients were severe (mRS score  $\geq 4$ ) during the course of the disease, while 86% of patients in the international cohort and 73% of the French patients reached a mRS score of 5 (5,15). Consistently, the Chinese study found a low frequency of intensive care unit admission (31% versus 75% in the other studies). This is explained by limited availability of medical recourses and concern of expenses, but it seems to be also related to a lower severity of the anti-NMDAR encephalitis in Chinese patients. Interestingly, these patients relapse as frequently, if not more, than the others [17.3% versus 15.5% in France (15) and 8% in the international cohort (5)], and the only factor associated with relapse that has been identified is the time to treatment, but not the treatment regimen nor the tumor status. This last point contrasts with the international study that has shown that patients without a tumor had a higher frequency of relapse than did those with a tumor, and that the use of immunotherapy was associated with fewer relapses. It is likely that the low frequency of tumors in Chinese patients leads to a lack of statistical power due to a too small number of patients in the tumor group.

The satisfactory outcome of Chinese anti-NMDAR encephalitis patients is certainly related to an effective management, comprising combined therapy of re-enforced first-line therapy and long-term immunotherapy. Indeed, repeated first-line immunotherapy was frequently used, whereas second-line immunotherapy was administered to a small portion of patients (7%), owing to the off-label use

of rituximab (RTX) for auto-immune encephalitis in China, cost, hospitalization requirements, and concerns about side effects. However, long-term immunotherapy was provided to 53.2% of patients, including mycophenolate mofetil (MMF) to 49.5% versus 6% in the international cohort (5) and 28% of the French patients (15). Given these results, one can naturally ask the question of the value of a second line of RTX immunotherapy in particular compared to a chronic immunosuppression by steroid sparing agents such as MMF or azathioprine (AZA), which is notably less expensive and well supported. The Chinese experience incites to further investigate the place of each of these therapies, maybe according to the severity of the disease and the presence or not of a controllable autoimmunity trigger.

The main limit of this real-life study is maybe its partially retrospective nature, however, the hindsight taken by Xu *et al.* on the evolution of practices under constraints, in particular financial and organizational, as illustrated by an eloquent figure on the percentages of correct diagnosis at the initial hospital visit over misdiagnosis over time, is particularly appreciated. Clearly, this work adds to the current knowledge of anti-NMDAR encephalitis and paves the way for future multicenter studies with more comprehensive evaluations, especially long-term cognitive ones.

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## Footnote

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*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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