



Original Article

Third-line tocilizumab for refractory pediatric anti-NMDA receptor encephalitis: a single-center case series

Rocio Victoria Garcia^{a,*}, Andrea del Rocio Quiroz Saavedra^b, Maria Celeste Buompadre^a, Maria Paula Ramos^a, Maria Luz Monti^a, Silvia N. Tenenbaum^a, Andrea G. Savransky^a

^a Department of Neurology, Hospital de Pediatría Prof. Dr. Juan P. Garrahan, Buenos Aires, Argentina

^b Hospital Real San José Valle Real, Zapopan, Jalisco, Mexico

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ABSTRACT

Tocilizumab has been proposed as a third-line therapy for refractory autoimmune encephalitis; pediatric Latin American data remain limited.

Objective: To evaluate the efficacy and safety of tocilizumab in pediatric patients with severe or refractory anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.

Materials and methods: We retrospectively reviewed pediatric patients with definite anti-NMDAR encephalitis treated with tocilizumab after inadequate response to previous therapy.

Results: Six patients (four males, median age at onset 4.5 years). All had severe disease (modified Rankin Scale [mRS] 4–5; Clinical Assessment Scale in Autoimmune Encephalitis [CASE] ≥ 10). All received first-line therapy, five received rituximab before tocilizumab. Tocilizumab was initiated 2–3 months after the last rituximab infusion. At 12 months, all achieved favorable outcomes (mRS 2; CASE ≤ 4). Adverse events included varicella-zoster virus infection, mild cytopenia, and dyslipidemia.

Conclusions: Tocilizumab was associated with favorable outcomes and acceptable safety in this small pediatric series of refractory anti-NMDAR encephalitis. The CASE scale was a sensitive and reliable instrument for longitudinal functional assessment.

1. Introduction

Autoimmune encephalitis (AE) is an immune-mediated disorder characterized by neuropsychiatric symptoms, movement disorders, and seizures associated with antibodies directed against the GluN1 subunit of the N-methyl-D-aspartate receptor (NMDAR) [1].

Compared with adults, pediatric patients have a lower frequency of associated tumors and generally show a better response to immunotherapy. Approximately 80% of patients achieve clinical recovery following immunotherapy and tumor resection when applicable [2].

Diagnosis is based on the clinical criteria proposed by Graus et al. in 2016³ and adapted for pediatric patients by Cellucci et al. in 2020 [4]. Definitive diagnosis is established by the detection of anti-NMDAR antibodies in cerebrospinal fluid (CSF) using a cell-based assay (CBA) [3,4].

First-line treatment consists of a combination of intravenous immunoglobulin (IVIG), intravenous methylprednisolone (IVMP), and

therapeutic plasma exchange (TPE). In patients who fail to achieve satisfactory functional recovery, treatment is escalated to second-line therapy with rituximab or cyclophosphamide. Nevertheless, up to 10% of patients remain refractory and require third-line therapeutic strategies [1].

Tocilizumab is a humanized monoclonal antibody targeting the interleukin-6 (IL-6) receptor, thereby inhibiting IL-6-mediated signaling [5]. Given the key role of IL-6 in the activation and differentiation of both B and T lymphocytes in autoimmune disorders, tocilizumab has shown efficacy in several immune-mediated diseases, including AE. In particular, its use has been reported in adults with AE refractory to rituximab [6].

However, data on the use of IL-6 inhibitors such as tocilizumab as third-line therapy in refractory pediatric AE remain limited. Although Latin American cohorts have described the epidemiology, antibody profiles, clinical features, and outcomes of AE in pediatric and adult populations, to our knowledge, no studies have specifically reported the

* Corresponding author at: Department of Neurology Hospital de Pediatría Prof. Dr. Juan P. Garrahan, Combate de los Pozos 1881, Buenos Aires, Argentina.

E-mail address: rociogarcia.neuro@gmail.com (R.V. Garcia).

use of tocilizumab in pediatric anti-NMDAR encephalitis in Latin America to date [7–9]. The aim of this study was to evaluate the efficacy and safety of tocilizumab in pediatric patients with severe or refractory anti-NMDAR AE.

2. Materials and methods

We conducted a retrospective review of pediatric patients treated at Hospital de Pediatría Prof. Dr. Juan P. Garrahan. Patients were included if they met the following criteria:

- 1. Age ≤ 17 years.
- 2. Diagnosis of definite anti-NMDAR encephalitis according to the pediatric diagnostic approach proposed by Cellucci et al. [4]
- 3. Detection of anti-NMDAR antibodies in CSF by CBA.
- 4. Treatment with first-line therapy, with or without second-line therapy.
- 5. Inadequate clinical response to first-line therapy and, when applicable, second-line therapy. Treatment response was assessed according to the international consensus recommendations [10]: Poor response was defined as a modified Rankin Scale (mRS) score > 2 or a Clinical Assessment Scale in Autoimmune Encephalitis (CASE) score > 9, evaluated two weeks after first-line immunotherapy or between three weeks and three months after initiation of second-line immunotherapy [11].
- 6. Treatment with tocilizumab.
- 7. A minimum follow-up period of 12 months after tocilizumab initiation.

Among 80 patients with suspected AE evaluated between January 2008 and December 2024, 46 tested positive for anti-NMDAR antibodies. Of these, six patients received tocilizumab and were included in this study.

2.1. Clinical assessment

Neurological disability and disease severity were assessed using the mRS [12] and the CASE [13,14]. Both scales were prospectively applied during treatment and follow-up by pediatric neuroimmunologists involved in patient care, at symptom onset, after each treatment line, immediately before tocilizumab initiation, and at 1, 3, 6, and 12 months after tocilizumab initiation. A concise comparison of the domains and scoring components of the mRS and CASE scale is provided in Table 1.

2.2. Paraclinical studies

Evaluated variables included CSF cytochemical findings, oligoclonal bands (OCBs) in paired CSF/serum samples assessed by isoelectric focusing, brain magnetic resonance imaging (MRI), and electroencephalographic (EEG) findings.

An AE antibody panel was performed in all patients using CSF samples analyzed by CBA, including antibodies against NMDAR,

contactin-associated protein-like 2 (CASPR2), gamma-aminobutyric acid type B receptor (GABA-B), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1 (AMPA1), AMPA2, leucine-rich glioma-inactivated protein 1 (LGI1), and dipeptidyl-peptidase-like protein 6 (DPPX).

The following infectious studies were performed in CSF: conventional bacterial cultures; polymerase chain reaction (PCR) testing for herpes simplex virus type 1 (HSV-1), HSV-2, human herpesvirus 6 (HHV-6), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and enterovirus; as well as mycobacterial and atypical pathogen cultures.

Tumor screening was performed in all patients at diagnosis and every 6 months for 2 years, including thyroid, testicular, or gynecologic ultrasound as appropriate, together with thoracoabdominal-pelvic computed tomography.

2.3. Treatment

- First-line therapy: IVIG 2 g/kg, IVMP 30 mg/kg/day, TPE, or a combination of these therapies.
- Second-line therapy: Rituximab, administered as intravenous induction therapy at 375 mg/m² per dose for four weekly doses.
- Third-line therapy: Tocilizumab, administered as two intravenous induction doses of 8 mg/kg in patients weighing >30 kg or 12 mg/kg in patients weighing <30 kg, given 15 days apart, followed by monthly infusions for ≥6 months.

2.4. Therapeutic response

Neurological functional outcome, assessed using the mRS, was categorized as favorable (score ≤ 2) or poor (>2). Disease severity according to the CASE was classified as mild (score 0–4), moderate (5–9), or severe (10–27). A favorable therapeutic response was defined as a reduction of at least 1 point in the mRS or 3 points in the CASE scale within 4 weeks after initiation of each treatment line.

Treatment non-response was defined in accordance with the 2021 international consensus recommendations [10]. Failure to improve after first-line therapy was defined as the absence of clinical improvement approximately 2 weeks after initiation of two or more first-line immunotherapies. Refractory disease after second-line therapy was defined as the absence of clinical improvement 1–3 months (typically >6 weeks) after initiation of the initial second-line therapy [11].

2.5. Drug safety

Adverse events related to tocilizumab administration were assessed during and after infusion, including infusion-related reactions, arterial hypertension, and infections. In addition, biochemical monitoring included complete blood cell count, liver function tests, and lipid profile evaluation.

Table 1
Clinical assessment scales used for longitudinal outcome evaluation.

Scale	Clinical construct assessed	Domains	Scoring	Interpretation	Outcome-based classification
Modified Rankin Scale (mRS)	Global functional disability	Overall degree of disability and dependence in daily activities	0–6	0: no symptoms. 1–2: no or slight disability. 3–5: moderate to severe disability. 6: death.	Favorable outcome: mRS ≤2. Poor outcome: mRS >2.
Clinical Assessment Scale in Autoimmune Encephalitis (CASE)	Disease severity in autoimmune encephalitis	Seizures, memory dysfunction, psychiatric symptoms, consciousness, language problems, dyskinesia/dystonia, gait instability/ataxia, brainstem dysfunction, and weakness	0–27	Each domain is scored from 0 to 3; higher scores indicate greater disease severity.	Mild: 0–4. Moderate: 5–9. Severe: 10–27.

3. Results

3.1. Demographic and clinical characteristics

During the study period, 80 patients with probable AE were evaluated in our pediatric neuroimmunology program. Among them, 46 tested positive for anti-NMDAR antibodies, whereas 34 were anti-NMDAR antibody-negative. Of the 46 patients with definite anti-NMDAR encephalitis, seventeen required second-line therapy. Among them, six had severe or refractory disease requiring escalation to tocilizumab and were included in this study.

Six patients (four males) with definite anti-NMDAR AE were included. Median age at presentation was 4.5 years (range 4–11 years). The remaining AE neuronal surface antibody panel was negative in all patients, and serum anti-myelin oligodendrocyte glycoprotein (MOG) antibodies were negative in the two patients tested.

The main demographic and clinical characteristics are summarized in Table 2.

Acute symptomatic seizures were the presenting symptom in all patients; four developed status epilepticus and one developed refractory status epilepticus. All patients presented with severe disease, with mRS scores of 4–5 and CASE scales ≥ 10 .

CSF analysis was abnormal in 5 of 6 patients, showing pleocytosis, while intrathecal OCBs were identified in 3 patients.

Brain MRI was abnormal in three patients, with the most frequent finding being T2/FLAIR hyperintensities involving the mesial temporal regions, particularly the hippocampi.

Initial EEG was abnormal in 5 of 6 patients, most commonly demonstrating focal or generalized slowing. Extreme delta brush was identified in only one patient.

3.2. Treatment

All patients received first-line therapy, including IVIG 2 g/kg, IVMP 30 mg/kg/day for 5–10 days, and TPE (3–10 procedures per patient).

Table 2

Demographic characteristics, ancillary studies, and treatments received in pediatric patients with anti-NMDAR autoimmune encephalitis treated with tocilizumab.

Characteristic	Patients (n = 6)
Sex, n	
Male	4
Female	2
Age at onset, years, median (range)	4.5 (4–11)
Abnormal CSF findings, n	5
Positive oligoclonal bands, n	3
Baseline brain MRI, n (%)	
Abnormal	3
Normal	3
Baseline EEG, n (%)	
Normal	1
Disorganized background activity	5
Focal slowing	1
Diffuse slowing	1
Epileptiform discharges	1
Electrographic seizures	1
Extreme delta brush	1
Treatments received, n (%)	
IVIG + IV methylprednisolone + TPE	6
Rituximab	5
Tocilizumab	6

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram; IV methylprednisolone, intravenous methylprednisolone; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; TPE, therapeutic plasma exchange.

Rituximab was administered in 5 of 6 patients; in the remaining patient, its use was contraindicated because of severe infectious complications related to TPE, including septic shock and multiorgan failure.

The mean time from initiation of first line-therapy to tocilizumab administration was 3.6 months (range 2–6 months), with a median of 3.5 months. In patients who received rituximab, the interval between the last rituximab dose and the first tocilizumab infusion was 2–3 months.

3.3. Follow-up

Functional outcome during clinical follow-up was assessed using the mRS scores and the CASE scale (Table 3).

Following first-line therapy, mRS scores remained unchanged in all six patients. In contrast, CASE scale showed a favorable response, defined as a reduction of at least 3 points, in 3 of 6 patients, whereas two patients remained unchanged and one worsened. However, all patients continued to have clinically relevant disease activity, with persistent moderate-to-severe impairment according to CASE scale (CASE >5) (Fig. 1).

Based on persistent disability and incomplete clinical recovery, treatment escalation was indicated in accordance with international consensus recommendations for pediatric anti-NMDAR encephalitis [7]. Rituximab was administered in five patients. In the remaining patient, rituximab was contraindicated because of severe infectious complications, and treatment was escalated directly to tocilizumab.

The five patients treated with rituximab showed persistent moderate-to-severe disease activity, with no significant improvement in

Table 3

Clinical characteristics, treatment, and outcomes in pediatric patients with anti-NMDAR encephalitis treated with tocilizumab.

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)/sex	4/M	5/M	11/M	4/F	7/M	4/F
Initial mRS/CASE	4/16	5/12	4/10	5/27	5/15	5/27
First-line therapy	IVIG + IVMP + TPE $\times 8$	IVIG + IVMP + TPE $\times 5$	IVIG + IVMP + TPE $\times 9$	IVIG + IVMP + TPE $\times 7$	IVIG + IVMP + TPE $\times 10$	IVIG + IVMP + TPE $\times 10$
mRS/CASE after first-line therapy	4/11	5/23	4/10	5/23	5/15	5/24
RTX	Yes	No	Yes	Yes	Yes	Yes
mRS/CASE after RTX	4/11	NA	4/9	5/23	5/15	5/24
Time from last RTX to TCZ (months)	3	NA	2	2	3	2
mRS/CASE at 1 month after TCZ	4/9	5/15	4/7	5/16	4/10	4/23
mRS/CASE at 6 months after TCZ	3/6	2/8	2/6	4/15	2/1	4/22
mRS/CASE at 12 months after TCZ	2/4	2/4	2/4	2/4	2/1	2/4
Treatment duration (months)	9	12	12	12	6	12

Abbreviations: CASE, Clinical Assessment Scale in Autoimmune Encephalitis; F, female; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; M, male; mRS, modified Rankin Scale; NA, not applicable; RTX, rituximab; TCZ, tocilizumab; TPE, therapeutic plasma exchange.

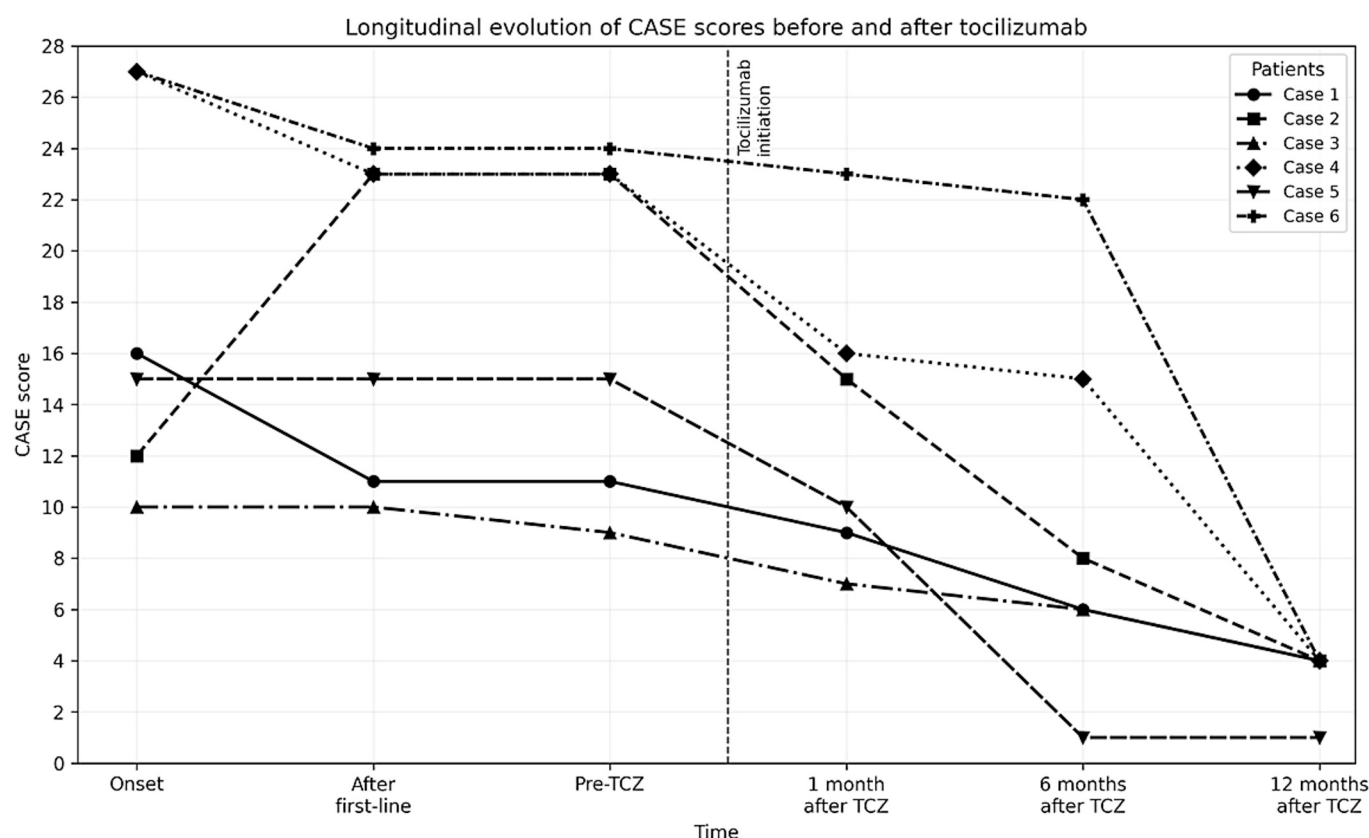


Fig. 1. Longitudinal evolution of CASE scores before and after tocilizumab initiation. CASE score trajectories from baseline to 12 months after tocilizumab initiation in six pediatric patients with anti-NMDAR encephalitis. CASE scores are shown at baseline, after first-line therapy, immediately before tocilizumab (TCZ) initiation (pre-TCZ), and at 1, 6, and 12 months after treatment initiation. The vertical dashed line indicates the start of tocilizumab therapy. Each line represents an individual patient.

either mRS or CASE scales at reassessment before tocilizumab initiation, performed 2–3 months after the last rituximab infusion (Table 3). These findings supported escalation to third-line therapy with tocilizumab.

Monthly tocilizumab treatment was discontinued after 6 months in one patient because of satisfactory functional recovery, with an mRS score of 2 and a CASE scale of 1. In the remaining five patients, treatment was continued.

In one patient, treatment had to be discontinued after 9 months because of VZV infection; however, the patient continued to improve clinically and achieved an excellent functional outcome at 12 months of follow-up (mRS 2, CASE 4).

The remaining four patients completed 12 months of tocilizumab therapy and achieved excellent functional recovery (mRS 2, CASE 4).

At the 12-month evaluation, all six patients continued to show abnormal EEG findings characterized by background disorganization or slowing. However, none developed epilepsy, as no further unprovoked seizures occurred, allowing withdrawal of antiseizure medications.

No neuroinflammatory relapses were observed in any of the six patients during follow-up.

3.4. Documented adverse events

Adverse events are summarized in Table 4. Only one patient developed an infectious complication, consisting of VZV infection, while no respiratory infections were observed. One patient developed mild thrombocytopenia ($122,000 \text{ cells/mm}^3$) and neutropenia (914 cells/mm^3); however, these abnormalities did not require treatment discontinuation. Another patient developed dyslipidemia with hypercholesterolemia (197 mg/dL), which was resolved with dietary management.

Table 4

Documented adverse events associated with tocilizumab.

Adverse event	Patients (n = 6)
Infusion-site reaction	0
Arterial hypertension	0
Infections	1
Cytopenias	1
Liver abnormalities	0
Dyslipidemia	1

4. Discussion

In this case series, we report six pediatric patients with severe or refractory anti-NMDAR encephalitis who required escalation to third-line therapy with tocilizumab, a humanized monoclonal antibody targeting the IL-6 receptor [6,14].

All patients presented with severe disease at onset, defined by marked functional disability on the mRS (scores 4–5) and severe disease activity on the CASE (scores ≥ 10). Acute symptomatic seizures were the initial clinical manifestation, consistent with findings from previous pediatric cohorts [4].

Evidence supporting tocilizumab in pediatric AE remains limited and is mostly derived from isolated case reports and small case series. Randell et al. reported three children with refractory AE who showed a rapid and sustained clinical response after tocilizumab, supporting its potential role as third-line therapy in selected pediatric patients, consistent with our findings [15]. Lee et al. reported that, among patients with AE who remained clinically refractory after first-line therapy and rituximab, escalation to tocilizumab was associated with better functional

outcomes than either additional rituximab treatment or observation without further immunotherapy [6].

Although a delayed effect of rituximab cannot be completely excluded, all patients fulfilled the international definition of refractory disease before treatment escalation. Clinical stabilization had persisted for 2–3 months after rituximab, a period exceeding the expected therapeutic window reported in previous pediatric studies. Therefore, escalation to tocilizumab was considered clinically justified.

From a pathophysiological perspective, anti-NMDAR encephalitis is primarily antibody-mediated, but accumulating evidence suggests that its immune mechanisms are not restricted to B-cell and plasma-cell autoantibody production. Cytokine and chemokine studies have demonstrated increased CSF levels of IL-6, IL-17, TNF- α , IL-10, IL-1 β , IL-12, and CXCL10, supporting the involvement of cytokine-mediated central inflammation and T-cell-related immune pathways. These findings provide a biological rationale for expanding immunotherapy beyond B-cell depletion in refractory patients, including therapeutic strategies targeting IL-6 signaling [16].

The adverse-event profile observed in our cohort was comparable to previous pediatric reports of tocilizumab. Respiratory infections have been described as the most common adverse event associated with this therapy [15]. Additional infections, cytopenias, liver enzyme abnormalities, dyslipidemia, hypertension, and infusion reactions have been described with tocilizumab [17,18]. In our series, most adverse events were manageable with monitoring and supportive measures, although one infectious complication required treatment discontinuation (Table 4). Thus, although careful monitoring is required, tocilizumab showed an overall acceptable safety profile in this small cohort.

In our cohort, mRS and CASE scales showed good correlation at baseline, when all patients had severe global disability. However, this association became less consistent during follow-up after tocilizumab initiation. While mRS scores showed only limited changes, CASE scales captured progressive improvement after successive infusions. This discrepancy may reflect the limited sensitivity of the mRS in pediatric anti-NMDAR encephalitis, as this scale provides a global measure of functional disability but does not specifically assess several core manifestations of the disease, including behavioral and psychiatric symptoms, language dysfunction, movement disorders, seizures, sleep disturbances, autonomic dysfunction, and cognitive recovery. In contrast, CASE scale evaluates multiple domains relevant to AE and may therefore be more sensitive for monitoring disease activity and therapeutic response over time. These findings are consistent with previous reports supporting the usefulness of CASE for longitudinal assessment in AE [14].

The duration of tocilizumab therapy ranged from 6 to 12 months, and all children ultimately achieved favorable functional outcomes and complete functional recovery.

Although the clinical improvement observed after tocilizumab may have been partially influenced by delayed effects of prior therapies, particularly rituximab, treatment escalation was considered justified based on the available evidence. Moreover, the therapeutic effects of rituximab in anti-NMDAR encephalitis are generally expected within the first 4–6 weeks, and the absence of clinical improvement beyond this period has been used to define treatment failure in previous studies [20,21]. In our patients, the lack of meaningful clinical improvement throughout the expected therapeutic window following rituximab fulfilled the consensus definition of refractory disease and supported escalation to tocilizumab as third-line therapy. Although a delayed effect of rituximab cannot be completely excluded, this limitation has been acknowledged in previous studies evaluating third-line therapies for AE [19,20].

An additional finding in our cohort was the persistence of EEG abnormalities. All patients continued to show EEG abnormalities at 12 months, characterized by background slowing or disorganization, despite favorable clinical recovery; however, none developed autoimmune-associated epilepsy, and antiseizure medications could be

withdrawn without seizure recurrence. EEG abnormalities are frequently reported in pediatric anti-NMDAR encephalitis, most commonly as focal or diffuse background slowing, sometimes associated with epileptiform activity [21]. Therefore, persistent background slowing or disorganization should not necessarily be interpreted as ongoing active encephalitis, particularly in the absence of unprovoked seizures, or other paraclinical evidence of sustained neuroinflammation [22].

Several Latin American cohorts have recently expanded the regional knowledge on AE, including multicenter studies describing clinical features, antibody profiles, and outcomes in pediatric and adult populations [7–9]. However, pediatric experience with third-line therapies, particularly tocilizumab, remains limited. In this context, the main contribution of our study is not only its regional perspective, but also the detailed longitudinal description of six children with severe or refractory anti-NMDAR encephalitis treated with tocilizumab, including systematic assessment of clinical outcomes using both mRS and CASE scales and reporting of treatment-related adverse events. To our knowledge, this is the first single-center Latin American pediatric series focused on tocilizumab in severe refractory anti-NMDAR encephalitis. Although limited by the small sample size and retrospective design, these findings support the potential role of tocilizumab as a promising third-line therapeutic option in selected children with severe anti-NMDAR encephalitis who do not respond adequately to first- and second-line therapies.

Several limitations of this study should be acknowledged. These include its retrospective design, the absence of a control group, the modest sample size, and the lack of formal neurocognitive assessments and measurement of disease-specific biomarkers, such as IL-6, in serum or CSF. In addition, this study was based on a pediatric neuroimmunology cohort rather than a hospital-wide encephalitis registry. Therefore, reliable data on the total number of infectious and non-infectious encephalitis cases evaluated at our institution during the study period were not available. As our hospital is a tertiary referral center, severe or refractory immune-mediated cases may be over-represented, which may limit the generalizability of our findings. Nevertheless, this study addresses a clinically relevant gap by providing detailed longitudinal data on third-line tocilizumab treatment, clinical outcomes, and safety in children with severe or refractory anti-NMDAR encephalitis.

5. Conclusion

Tocilizumab was associated with favorable clinical outcomes in this cohort of children with severe anti-NMDAR encephalitis who had failed previous therapies. Tocilizumab appeared to be an effective therapeutic option in this series of pediatric patients, with an overall favorable safety profile. In addition, our findings support the CASE scale as a sensitive and reliable instrument for longitudinal functional assessment in patients with AE, as it detected clinically meaningful changes that were not captured by the mRS during follow-up.

Although prospective multicenter studies are needed, our findings support IL-6 blockade as a biologically plausible therapeutic strategy after B-cell depletion failure and provide the first pediatric Latin American experience with tocilizumab in refractory anti-NMDAR encephalitis.

Authors contribution

Rocio Victoria Garcia designed the study, collected the data, analyzed the data, and wrote the manuscript.

Andrea del Rocio Quiroz Saavedra assisted with data collection, data analysis, interpretation and revision of the manuscript.

Maria Celeste Buompadre contributed to study design, data analysis, and edited the manuscript.

Maria Paula Ramos contributed to study design, data analysis, and

edited the manuscript.

Maria Luz Monti contributed to data analysis and edited the manuscript.

Silvia N Tenenbaum contributed to data analysis, revision and interpretation of neuroimaging studies, and edited the manuscript.

Andrea G Savransky had a major role in drafting/revision of the manuscript for content, including medical writing for content; major role in data acquisition; analysis or interpretation of data; revision and interpretation of neuroimaging studies.

Statements and declarations

Consent to participate

The requirement for informed consent was waived by the Institutional Review Board due to the retrospective nature of the study and because all patients received standard-of-care treatment.

Ethical considerations

The study was approved by the Institutional Review Board/Ethics Committee of Hospital de Pediatría Prof. Dr. Juan P. Garrahan. Due to the retrospective observational design of the study and because all patients received standard-of-care treatment, the requirement for informed consent was waived. Patient confidentiality and data anonymization were maintained throughout the study in accordance with the principles of the Declaration of Helsinki.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Silvia N Tenenbaum has served as an advisor on scientific advisory boards for Genentech-Roche and Alexion Pharmaceuticals, and has received speaker honoraria from F. Hoffmann-La Roche and Novartis Argentina. The remaining authors declare no conflicts of interest related to this study.

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