Anti –NMDA receptor encephalitis in children: A study from Eastern India

***Sananda Pati[1], Mrinalkanti Das[2], Arpan Saha[3], Ranjabati Datta[3], Soumi Bag[3], Saraswati Mondal[3]**

Sri Lanka Journal of Child Health, 2022; **51**(4): 513-518
DOI: http://dx.doi.org/10.4038/sljch.v51i4.10363

Abstract

Introduction: Anti-N-methyl-d-aspartate receptor (Anti-NMDAr) encephalitis is the second common cause of autoimmune encephalitis.

Objectives: To describe the clinico-epidemiological profile, treatment, and outcome of paediatric anti-NMDAr encephalitis patients.

Method: This is a retrospective, observational study in a tertiary care hospital from eastern India with 16 anti-NMDAr encephalitis cases aged <12 years. All patients were positive for cerebrospinal fluid (CSF) anti NMDAr antibody. Graus criteria were used for case detection and modified Rankin scale for assessing neurological disability before and after treatment. All cases received first line immunotherapy with intravenous immunoglobulin (IVIG), methyl prednisolone or both; those with failure to respond or worsening were considered for second line immunotherapy.

Results: The 16 patients were aged 6 months to 11 years (mean 7.7 years); 43.8% were female; they were diagnosed by an average 25 days; speech defects (93.8%), psychiatric manifestations (100%) and seizures (87.5%) were the early features. CSF anti NMDAr antibody was positive in 100% and electro-encephalographic (EEG) changes were found in 100%. There were no tumours in pelvis or abdomen on ultrasonography. Magnetic resonance imaging abnormalities were present in 62.5%. First line immunotherapy consisting of only IVIG (18.8%), only methyl prednisolone (6.25%) and both IVIG and methyl prednisolone (75%) was started by a median 30 days, with better response in the latter group. Seven (43.8%) patients received second line immunotherapy (Rituximab) with prompt response.

Twelve (75%) cases are under regular follow up. Oral prednisolone was continued for one year in the initial 8 cases. In the remaining 4 cases, steroids were tapered when serum anti NMDAr antibody became negative. Relapse was noted in one case

Conclusions: Speech defects (93.8%), psychiatric manifestations (100%) and seizures (87.5%) were early features. Positive CSF anti NMDAr antibody and EEG changes were found in 100%. First line immunotherapy consisted of IVIG and methyl prednisolone.

(Key words: Autoimmune encephalitis, Anti NMDAr antibody, Modified Rankin scale, Graus criteria)

Introduction:

Anti-N-methyl-d-aspartate receptor (Anti-NMDAr) encephalitis is considered the second common autoimmune encephalitis[1,2]. It is a comparatively new entity[3,4] described with a wide range of symptoms from psychiatric manifestations, seizures, altered sensorium and choreo-athetoid movements to autonomic disturbances and a potentially fatal outcome if left undiagnosed and untreated[5,6]. There are several large-scale studies done in the western world [3-7]. However, there are only a few studies from India[8-12] and hardly any from eastern India.

Objectives

To study the clinico-epidemiological profile of Anti NMDAr encephalitis in paediatric patients (<12 years of age), their immediate response to immunotherapy, outcome and follow up.

Method

A retrospective observational single centre study was done in a tertiary care hospital of eastern India from February 2016 to February 2021. Only cases of anti-NMDAr encephalitis diagnosed by the presence of anti-NMDAr antibody in the cerebrospinal fluid (CSF), treated and followed up in the department of paediatrics of our hospital during the study period, were included. There were 16 such cases whose complete records were traced.

The data were collected from the hospital records and outpatient department follow up of each patient

[1]*Assistant Professor,* [2]*Professor,* [3]*Ex Postgraduate Trainee, Department of Paediatric Medicine, IPGME & R and SSKM Hospital, Kolkata, India*
**Correspondence:* sanandapati@gmail.com
https://orcid.org/0000-0002-2455-4089

(Received on 11 February 2022: Accepted after revision on 18 March 2022)
The authors declare that there are no conflicts of interest
Personal funding was used for the project.

and recorded in predesigned proforma. Apart from procuring the Bed Head Tickets (BHTs) we gathered information from the Discharge Summaries, which, along with relevant investigations, are given to the patients in the form of Discharge Certificates. These are archived by us. These are also brought by patients at time of follow up. Electroencephalograms (EEGs) are recorded in the BHTs as well as Discharge Certificates.

The six clinical features mentioned by Graus F, *et al*[6] namely, psychiatric manifestations, speech abnormalities, seizures, abnormal movements, impaired consciousness, and autonomic disturbances were recorded. Other clinical features, like fever, ataxia and hemiparesis, if present were also noted. Investigations included complete blood counts, liver and renal function tests, blood gas analyses, serum caeruloplasmin serology and antinuclear antibodies (ANA) / anti–thyroperoxidase antibody (Anti-TPO Ab) levels, CSF study for cytology, protein and sugar estimation and serology of Japanese encephalitis Ab, anti-NMDAr Ab and herpes simplex virus 1 & 2 polymerase chain reaction study. CSF anti-NMDAr Ab positivity (by indirect immunofluorescence method) was considered diagnostic for anti-NMDAr encephalitis. Magnetic resonance imaging (MRI) of brain, EEG, ultrasonography (USG) of whole abdomen to look for abdominal, pelvic, or testicular tumours were included. Serum anti-NMDAr Ab levels were checked during follow up at 3, 6, 9 and 12 months.

The cases received first line immunotherapy with either intravenous immunoglobulin (IVIG) 2g/kg over 5 days alone or a combination of IVIG and Inj pulsed methylprednisolone 30mg/kg/daily for 5 days. Response to treatment was assessed using modified Rankin scale for neurological disability[5,13]. At least 2-point improvement in modified Rankin scale (mRs) for neurological disability or a minimum score of 2 in mRs within four weeks of starting immunotherapy was considered an adequate response. Those with inadequate response or worsening were considered for second line immunotherapy with Inj Rituximab[1,5,14,15]. Patients were followed up after discharge to look for relapses, residual disability and improvement of psychiatric abnormalities like emotional lability. The outcome was recovered with minimal or no disability, relapse, lost to follow up or death.

Ethical issues: Approval was obtained from the Ethics Committee of the Institute of Post Graduate Medical Education and Research, Kolkata, India (IPGME&R/IEC/2021/274). Being a retrospective study, informed consent was not feasible.

Results

Of the sixteen patients 9 (56.2%) were male and 7 (43.8%) were female. Their age range was 6 months to 11 years with a mean of 7.7 years. They had normal development, memory, and intelligence prior to this illness. All patients were referred to our hospital in the 1st to 8th week of illness. Anti NMDAr encephalitis was suspected based on typical clinical features (Table 1 and Figure 1).

Table 1: ***Clinical features of the cases***

Cases	Age/Sex	Speech defects	Psychiatric manifestations	Seizures	Autonomic manifestations	Glasgow Coma Scale (GCS) <8	Abnormal movements	Others
1	6yrs/F	+	+	-	-	+	+	-
2	3.5yrs/M	+	+	+	-	-	+	-
3	10yrs/M	+	+	+	-	+	+	-
4	11yrs/M	-	+	-	-	-	-	-
5	2yrs/F	+	+	+	+	+	+	Fever
6	11yrs/F	+	+	+	+	+	+	Fever, hemiparesis
7	5yrs/F	+	+	+	+	+	+	Hemiparesis
8	10yrs/M	+	+	+	+	+	+	-
9	11yrs/F	+	+	+	+	+	+	Fever
10	10yrs/M	+	+	+	+	+	+	Fever
11	7yrs/M	+	+	+	+	+	+	Fever
12	9yrs/M	+	+	+	-	-	+	-
13	3yrs/F	+	+	+	-	+	+	-
14	7mths/M	+	+	+	-	+	+	-
15	10yrs/F	+	+	+	+	+	+	-
16	8yrs/M	+	+	+	-	-	+	-

Note: Case no. 4 had purely psychiatric manifestations and subacute presentation. GCS<8 signifies altered sensorium.

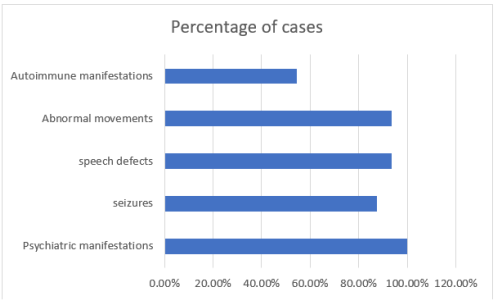

Figure 1: ***Bar diagram showing distribution of clinical features***

Diagnosis was made by 2nd to 4th week of illness in most of the cases (mean=25 days). It was delayed in the patient with pure psychiatric manifestations (case no. 4). The average duration of hospitalization was 6 weeks. Speech defects were present in 93.8% cases. It was an early feature occurring in days 2-3 of illness. Psychiatric manifestations were present in all cases (100%) on day 2-3 of illness. Agitation, irritability, and insomnia (36.7%) were common in younger children. Lapses in working memory, recent memory and emotional lability (63.3%) were seen in older children. One 11-year-old child (case No. 4) was mono-symptomatic with psychiatric manifestation for two months.

Seizures were present in 14 (87.5%) children by day 1 to 4 of illness; generalised tonic-clonic seizures (GTCS) were present in 5 (35.7%) and focal seizures in 9 (64.3%). Sensorium was altered early by day 4-5 in twelve (75%) patients with decreased responsiveness, lethargy, and progressive downhill course. Abnormal movements were present in 15 (93.8%) patients. It was a relatively late presentation at day 7-10. Orofacial dyskinesia was most common (50%) followed by choreoathetoid movements. Eight (50%) of our cases had autonomic features consisting of hypertension, sweating and sialorrhoea singly or in combination. Distribution of clinical features are shown in Figure 1.

Apart from these clinical features (Graus clinical criteria), fever was present in the prodromal period in 5 (31.3%) children. Hemiparesis was present in three. The disease process was rapidly progressing in 12 (*75%*) patients with a modified Rankin scale (mRs) score of 4-5 before immunotherapy was started. In all cases, CSF study showed mild mononuclear pleocytosis with slight rise of protein and positive Anti NMDAr ab (NR 1). Also diffuse slowing in the EEG was present in all cases. MRI of brain had discrete areas of altered signal intensity hypo to iso in T1, hyper in T2, and flare with diffusion restriction in different locations (parietal lobe 5, temporal lobe 4 and cerebellar hemisphere 1) in ten cases (62.5%). USG of abdomen did not find any abdominal or pelvic space occupying lesion. All other investigations revealed no abnormality.

First line immunotherapy was started by day 8 to 60 of illness (median 25 days). Three (18.8%) patients received IVIG alone of whom 1 improved, 1 had equivocal response and 1 expired. One patient received Inj. methyl prednisolone alone. Twelve (75%) patients received both IVIG and Inj. methyl prednisolone simultaneously and four of them (50%) showed remarkable improvement. The average time to response to 1st line immunotherapy was 2 weeks after starting treatment. Seven (43.8%) of our patients received second line immunotherapy with Inj. Rituximab (375mg/$m^{2,}$ weekly, 4 doses) due to rapid deterioration even after 1st line immunotherapy (sequential IVIG and methyl prednisolone). Prompt response was noted in three cases. One patient left (case no.9*)* after receiving 1st dose of Inj Rituximab. None of our patients received plasmapheresis. Table 2 shows time to diagnosis, treatment received and outcome.

Table 2: Investigations leading to diagnosis, treatment and outcome

Cases	Age/Sex	CSF Anti-NMDAR antibody	EEG Diffuse slowing	*MRI brain	Definite diagnosis made by	First line immune-therapy	Second line immune-therapy	Outcome	Follow up (months)
1	6yrs/F	+	+	NA	Day 32	IVIG +Met Pred	None	Recovered	55
2	3.5yrs/M	+	+	+	Day 20	IVIG only	None	Recovered	51
3	10yrs/M	+	+	+	Day 17	IVIG only	None	Died	-
4	11yrs/M	+	+	+	Day 60	IVIG only	None	No f / up	-
5	2yrs/F	+	+	NA	Day 15	IVIG +Met Pred	Rituximab	Recovered	40
6	11yrs/F	+	+	+	Day 30	IVIG +Met Pred	None	Recovered	33
7	5yrs/F	+	+	+	Day 19	IVIG +Met Pred	None	Recovered	22
8	10yrs/M	+	+	NA	Day 21	IVIG +Met Pred	None	Recovered	17
9	11yrs/F	+	+	NA	Day 19	IVIG +Met Pred	Rituximab	Left	-
10	10yrs/M	+	+	+	Day 13	IVIG +Met Pred	Rituximab	Recovered	12
11	7yrs/M	+	+	+	Day 14	IVIG +Met Pred	Rituximab	Recovered	12
12	9yrs/M	+	+	NA	Day 25	Met Pred	None	Recovered	11
13	3yrs/F	+	+	+	Day 30	IVIG +Met Pred	Rituximab	Relapsed	10
14	7mths/M	+	+	+	Day 30	IVIG +Met Pred	None	Recovered	10
15	10yrs/F	+	+	+	Day 25	IVIG +Met Pred	Rituximab	Left	-
16	8yrs/M	+	+	NA	Day 30	IVIG +Met Pred	Rituximab	Recovered	08

*Note: *MRI Brain-10 patients have abnormal brain imaging (+) findings Altered signal intensity in T1&2 and flare in DWI while 6 had no abnormality (NA). EEG showed spike and slow waves*

Maintenance therapy was continued with a daily dose of steroids. Prednisolone was started at 2mg/kg and gradually tapered. Low doses were continued up to 1 year in the initial 4 cases. Serum Anti NMDAr ab negativity correlated well with disease remission. So, we used serum Anti NMDAr ab levels to guide steroid tapering and duration of therapy in the later 8 cases. Only one relapse was noted in this group. It was treated by re-instigating 1st line immunotherapy with prompt response.

Twelve (75%) cases are on regular follow-up. Relapse was noted in 1 case during this period. No residual disability at 6-month follow-up (mRs score 1) was found in other cases. Emotional lability and behavioural abnormality showed slow recovery. Repeat EEG was done in 5 cases at 1 year follow up and was found to be within normal limits.

Discussion

In our study we have used Graus clinical criteria for early recognition of Anti NMDAr encephalitis. Modified Rankin Scale (mRs) was used for assessment of severity of disease and response to treatment, as done in other studies by Titulaer MJ, *et al*[5] and Nagappa M, *et al*[5,8]. Speech defects, psychiatric manifestations and seizures were the early features noted at day 2-3 of illness. Seizures were present in 87.5 % of children in our study. GTCS was present in 35.7% cases and focal seizures in 64.3%. The seizures were refractory to treatment with antiepileptics in 5 (35.7%) cases and responded to immunotherapy eventually. Titulaer MJ, *et al*[5] had 111 children in the under 12 age group, 50% of whom had seizures. Speech defects in different forms like expressive aphasia, mutism, incoherent speech and echolalia were present in all cases. Psychiatric manifestations were common (100%). In accordance with previous studies[1,5] we found them to be more prominent in older children. However, agitation, irritability and insomnia were common in younger children (36.7%). Changes in personality, memory deficits and emotional lability were present in older children (63.3%). Case no. 4 presented with psychiatric manifestation and was on antipsychotics for two months without improvement. His EEG showed diffuse slowing and Anti NMDAr antibody was positive in CSF clinching the diagnosis.

Most of the patients were referred to us from other hospitals without suspicion of this entity resulting in delayed diagnosis. The disease had a rapid progression in ten (75%) patients with mRs score of 4-5 except in Case no.4 who had a subacute course. Previous studies [5-7] had shown abnormal movements like dystonia, tremors, choreoathetoid movements, facial tics and orofacial dyskinesia to be common in the paediatric age group. In our case series too, we found abnormal movements to be very common (93.8%) but a relatively late presentation at day 7-10 of the illness. Autonomic features are characteristic of anti-NMDAr encephalitis but are more prevalent in the adult populations[1,5-7]. The autonomic features that can be present are central hypoventilation, hypertension, bradycardia, tachycardia, sialorrhoea and sweating. Eight of our cases had autonomic features. Apart from these clinical features (Graus clinical criteria), fever was present in the prodromal period in five children and hemiparesis in three.

Extreme delta brush pattern, which is the classical EEG finding in anti-NMDAr encephalitis was not found in any of the cases but diffuse slowing was seen in all cases. It normalized post treatment at the one year follow up. MRI of the brain was abnormal in 10 (62.5%) cases in this study but Titulaer MJ, *et al*[5] observed changes in only 40% cases, while Dalmau J, *et al*[7] found changes in 50%. Rutatangwa A, *et al*[17] pointed out the importance of timing of MRI of the brain in their case series. According to them it could be normal at presentation, with abnormalities appearing later, as the disease progressed.

Immunosuppression and tumour resection are the mainstay of therapy in autoimmune encephalitis[1,5,14,15]. First-line immunotherapies used are corticosteroids (intravenous and oral), IVIG and/or plasma exchange[14]. IVIG is a costly drug and sometimes in short supply in a Government Hospital set up like ours. Thus Inj. methyl prednisolone alone was started in some patients. Second-line treatment is usually administered when the response to first-line therapy is inadequate (guided mRs) or when the disease is known to be severe or relapsing. It typically includes rituximab, cyclophosphamide, azathioprine, and mycophenolate mofetil as per current studies[14,15]. Death rate can be as high as 20% in those who fail 1st line immunotherapy and do not receive 2nd line immunotherapy[5,14]. All the patients in our cohort responded to 1st line or 2nd line immunotherapy and so we did not use plasmapheresis.

We found better outcome with simultaneous use of IVIG and pulsed methylprednisolone rather than use of a single drug as 1st line immunotherapy. Three out of four patients treated with Rituximab as 2nd line immunotherapy had excellent results. Similar observations were found in other studies[5,8,14,15]. Improvement was slow and patients took 2-6 months after discharge for complete recovery. Motor recovery was earlier compared to mental recovery as was evident from mRs score 0-1 at the 6 months follow up. However, higher functions and psychiatric manifestations like memory, speech and emotional lability took a greater time to normalize. Repeat EEGs (5 patients) were normal at the one year follow up. Repeat serum Anti NMDAr ab was done at 3, 6, 9 and 12 months follow up.

Serum Anti NMDAR ab negativity was used to taper steroid treatment in the last 8 cases. One case relapsed during follow up at 3 months of the initial episode. First episode was treated with 1st and 2nd line immunotherapy and relapse with repeat 1st line immunotherapy. Gresa-Arribas N, *et al*[16] in their retrospective study have shown CSF Anti NMDAr ab titres correlate better than serum Anti NMDAr ab titres and are better indicators of prognosis and relapse. Lumbar puncture being an invasive procedure and due to resource constraint, CSF Anti NMDAr ab was not checked during follow up in our study.

This study has its limitations. It is a retrospective study in a single centre with a small sample size. Serial CSF Anti NMDAr antibody levels were not done during follow up. Quantitative estimation of anti NMDAr antibody was not done. During the 5-year study period the mainstay of treatment of Anti-NMDAr encephalitis remained immunotherapy. However, newer guidelines have emerged making the management more streamlined and clarifying things like time to start 2nd line immunotherapy, maintenance therapy, treatment of relapses etc. This is a confounding factor in the analysis which is a limitation.

Conclusions

Speech defects (93.8%), psychiatric manifestations (100%) and seizures (87.5%) were the early features. Positive CSF anti NMDAr antibody and EEG changes were found in 100%. First line immunotherapy consisted of IVIG and methyl prednisolone.

References

1. Armangue T, Dalmau J, Autoimmune Encephalitis. In: Kliegman R, Stanton B, St. Geme J. W, Schor N. F, Behrman R. E, Eds. Nelson Textbook of Pediatrics, 21st ed. Philadelphia, USA: Elsevier, 2019. pp. 3179-82.

2. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, *et al.* Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infectious Diseases* 2010; **10**: 835–44. https://doi.org/10.1016/S14733099(10)70222-X

3. Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. *Annals of Neurology* 2005; **58**: 594–604. https://doi.org/10.1002/ana.20614 PMid: 16178029 PMCid: PMC2245881

4. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, *et al.* Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Annals of Neurology* 2007; **61**(1): 25–36. https://doi.org/10.1002/ana.21050 PMid: 17262855 PMCid: PMC2430743

5. Titulaer MJ, McCracken L, Gabilondo I, Armange T, Glaser C, Lizuka T, *et al.* Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurology* 2013; **12**(2): 157–65. https://doi.org/10.1016/S14744422(12)70310-1

6. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Celluci T, *et al.* A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurology* 2016; **15**(4): 391–404. https://doi.org/10.1016/S14744422(15)00401-9

7. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurology* 2011; **10**: 63-74 https://doi.org/10.1016/S14744422(10)70253-2

8. Nagappa M, Bindu PS, Mahadevan A, Sinha S, Mathuranath PS, Taly AB. Clinical features, therapeutic response, and follow-up in paediatric Anti-N-Methyl-d-Aspartate Receptor encephalitis: Experience from a tertiary care University Hospital in India. *Neuropediatrics* 2016; **47**(1): 24-32. https://doi.org/10.1055/s-0035-1569464 PMid: 26727295

9. Nair AV, Menon J, Kuzhikkathukandiyil P. Clinical profile and neuropsychiatric outcome in children with Anti-NMDAR Encephalitis. *Indian Pediatrics* 2019; **56**: 247-9. https://doi.org/10.1007/s13312-019-1509-3 PMid: 30955001

10. Goenka A, Jain V, Nariai H, Spiro A, Steinschneider M. Extended clinical spectrum of anti-N-methyl-D-aspartate receptor encephalitis in children: A case series. *Pediatric Neurology* 2017; **72**: 51-5. https://doi.org/10.1016/j.pediatrneurol.2017.03.010
PMid: 28506503

11. Basheer S, Nagappa M, Mahadevan A, Bindu PS, Taly AB, Girimaji SC. Neuropsychiatric manifestations of paediatric NMDA receptor autoimmune encephalitis: A case series from a tertiary care center in India. *Primary Care Companion for CNS Disorders* 2017; **19**(4): https://doi.org/10.4088/PCC.17m02110
PMid: 28841275

12. Goenka A, Jain V. Anti-NMDA receptor encephalitis. *Indian Journal of Pediatrics* 2016; **83**:1032. https://doi.org/10.1007/s12098-016-2147-6
PMid: 27206686

13. Broderick JP, Adeoye O, Jordan E. Evolution of the modified Rankin Scale and its use in future stroke trials. *Stroke* 2017; **48**:2007–12. https://doi.org/10.1161/STROKEAHA.117.017866
PMid: 28626052 PMCid: PMC5552200

14. Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: A systematic review. *Expert Review of Neurotherapeutics* 2015; **15**: 1391-419. https://doi.org/10.1586/14737175.2015.1115720
PMid: 26559389

15. Remy KE, Custer JW, Cappell J, Foster CB, Garber NA, Walker LK, *et al.* Pediatric Anti-N-Methyl-d-Aspartate Receptor encephalitis: A review with pooled analysis and critical care emphasis. *Frontiers in Pediatrics* 2017; **5**: 250. https://doi.org/10.3389/fped.2017.00250
PMid: 29226117 PMCid: PMC5705558

16. Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt S, *et al.* Antibody titers at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurology* 2014; **13**: 167–77. https://doi.org/10.1016/S14744422(13)70282-5

17. Rutatangwa A, Mittal N, Francisco C, Nash K, Waubant E. Autoimmune encephalitis in children: A case series at a Tertiary Care Centre. *Journal of Child Neurology* 2020; **35**(9): 591-9. https://doi.org/10.1177/0883073820923834
PMid:32458722