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ORIGINAL COMMUNICATION

Cognitive and neuropsychological evolution in children with anti-NMDAR encephalitis

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Abstract We describe neurological and cognitive/neuropsychological changes from symptom onset in 13 consecutive children (8 females and 5 males; median age 11 years, range 3–17) with anti-NMDAR-encephalitis. We assessed neurological status using the modified Rankin Scale for children and cognitive/neuropsychological status using a standardized battery that was administered serially in 10 prospective patients, and at latest follow-up in three retrospective patients diagnosed before study initiation. Symptom onset was marked by neurological or psychiatric/behavioural manifestations, which became severe but regressed at variable rates after starting immunotherapy. The 10 prospective patients were able to undergo first standardized cognitive/neuropsychological assessment a median of 3 months (range 1–12) after symptom onset: they had extensive deficits, although severity varied. Subsequent assessment showed marked improvements although the timescale varied. At latest evaluation (median 31 months, range 3–112, after symptom onset), seven patients had no neurological disability, five had improved substantially, and one had persistent behavioural problems. Latest cognitive/neuropsychological assessment in 11 patients with at least a year of follow-up showed normal general intellectual abilities, but over half had residual deficits indicating frontal lobe dysfunction. All patients had resumed normal activities. Our findings suggest that early installation of immunotherapy results in good long-term recovery in most paediatric patients with anti-NMDAR-encephalitis, however, recovery is incomplete and the disease leaves subtle lasting defects that impact quality of life, social relationships, and academic achievement.

Keywords Anti-NMDAR encephalitis · Paediatric patients · Cognitive functioning · Long-term outcomes

Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a treatable disease characterized by fairly abrupt onset of a constellation of symptoms attributable to diffuse brain dysfunction [1, 2]. Anti-NMDAR encephalitis was first described in 2007 as a paraneoplastic condition associated with ovarian teratoma in young women [3]; it is now increasingly recognized in children and adolescents with no detectable tumour [4–6]. Despite improved understanding of the disorder [4–9], few data on its cognitive/neuropsychological evolution are available [10–12]. The aim of the present study was to describe the evolution of neurological and cognitive/neuropsychological functioning in paediatric patients with anti-NMDAR-encephalitis.

Methods

Participants

The series comprised 13 consecutive patients (8 females and 5 males), median age 11 years (range 3–17 years) at

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symptom onset, diagnosed with anti-NMDAR encephalitis between 2007 and 2014, and followed at the Department of Pediatric Neuroscience, Foundation IRCCS Neurological Institute "C. Besta", Milan. Diagnosis was based on clinical findings and presence of anti-NMDAR antibodies (detected by indirect immunofluorescence) in serum and cerebrospinal fluid (CSF). All patients underwent serial video-EEG recordings and brain magnetic resonance imaging (MRI), and were screened at least once for tumours. In 10 prospectively recruited patients, neurological status was assessed soon (4 weeks) after symptom onset and regularly thereafter. For three other patients, already in follow-up (from disease onset) when the study was conceived, early neurological status was assessed from clinical records. Neurological disability was assessed with the modified Rankin Scale for Children (mRS) [13], with improvement defined as decrease by at least 1 mRS point.

Cognitive and neuropsychological assessments

The 10 prospectively recruited patients (patients 1–10) received serial assessments of cognitive/neuropsychological functions using a standardized battery. The first assessment was as soon as possible after the initiation of immunotherapy, with additional assessments planned every 6 months to 2 years, and yearly thereafter. The three retrospectively recruited patients (patients 11–13) only received a single standardized cognitive/neuropsychological assessment a median of 85 months after symptom onset. The battery employed validated Italian versions of standard instruments, and assessed six domains:

1. General intellectual abilities: Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III); Wechsler Intelligence Scale for Children, 3rd edn. (WISC-III); Wechsler Intelligence Scale for Children, 4th edn. (WISC-IV); Wechsler Adult Intelligence Scale-Revised (WAIS-R); Leiter International Performance Scale-Revised (Leiter-R); and Griffiths Mental Development Scales 2–8 (GMDS 2–8);
2. Receptive and expressive language: expressive vocabulary—Naming Tests (BVN 5–11, BVN 12–18); verbal comprehension—Token Test for Children, 2nd edn. (TTFC 2), Test for Reception of Grammar (TROG); phonemic and semantic verbal fluency (BVN 5–11, BVN 12–18);
3. Short-term verbal memory (Digit Span—a Wechsler subtest) and short-term visuo-spatial memory (Corsi's Block Tapping Test Forward—BVN 5-11, BVN 12-18);
4. Planning (Tower of London—TOL) and Block Design—a Wechsler subtest);
5. Selective and sustained attention (Barrage Task, Bell Test, and Coding—a Wechsler subtest);
6. Visual-motor integration (Copying Form Test of Developmental Test of Visual-Motor Integration, and Rey–Osterrieth Complex Figure (ROCF) test.

Data analysis

Continuous variables were summarized as medians and ranges. Results for general intellectual abilities (Table 1) were converted into standard scores with values below 85 considered below normal. Scores for the neuropsychological instruments (Table 2) were age-corrected and converted into z scores, percentiles, or weighted scores, as appropriate, using published normative data. The z score indicates the deviation (in units of standard deviation) from the mean population score which is set to zero. A z score of -2 (or less) comprises 2.5 % of the normal distribution and is considered to be significantly lower than average. However, we arbitrarily considered a z score of -1.6 as below normal. Similarly, percentiles of 10 % or lower, and weighted scores of 8 or lower, were also considered below normal.

Results

Median length of follow-up was 31 months (range 3–112 months).

Clinical characteristics and response to treatment

Symptom onset was marked by neurological manifestations (seizures, movement disorders, or psychomotor regression) in 9 patients (patients 1–3, and 7–12) (Tables 1, 2); and by severe psychiatric and behavioural symptoms (anxiety, depressed mood, temper tantrums, inappropriate behaviour, paranoid thoughts, delusions and hallucinations) in 4 (patients 4–6, and 13). Neurological impairment was moderate or severe (mRS score above 4) in 7 patients (patients 3, 4, 6, 7, 9, 10, and 12; median mRS score 5) and intensive care was required for patient 6.

Within 4 weeks of onset, all the patients had at least 4 of the typical symptoms of anti-NMDAR encephalitis (seizures, movement disorders, psychiatric and behavioural symptoms, psychomotor regression, cognitive impairment, language disintegration, loss of short-term memory, sleep disturbance, autonomic dysfunction, and loss of contact) [5]. Eight patients (patients 3, 4, 6–10, and 12) rapidly lost the ability to attend to bodily needs, and eat and walk unassisted. Episodes of decreased responsiveness occurred in 6

Table 1 Serial assessment of general intellectual abilities in patients with anti-NMDAR encephalitis

Patient, Gender	Age at symptom onset	Time from symptom onset to assessment	GENERAL INTELLECTUAL ABILITIES (standard scores)						
Time 1									
1, F	7y 5m	1 m	**WISC IV**	FSIQ 106	VCI 84	PRI 106	WMI 112	PSI 112	
2, F	11y	1 m	**WISC IV**	FSIQ 86	VCI 82	PRI 111	WMI 88	PSI 74	
3, F	11y 4m	1.5 m	**WISC IV**	FSIQ 53	VCI 88	PRI 63	WMI 52	PSI 47	
4, F	16y 6m	2 m	**WISC III**	FSIQ 54	VIQ 65	PIQ 53			
5, F	14y	3 m	**WISC IV**	FSIQ 42	VCI 66	PRI 45	WMI 55	PSI 59	
6, M	17y 5m	3 m	**WAIS-R**	FSIQ 75	VIQ 79	PIQ 75			
7, M	3y 6m	3 m	**GMDS 2-8**	Locomotor 98	Personal-social 73	Language 64	Eye-hand co-ordination 60	Performance 58	Practical reasoning 60
8, M	5y 7m	6 m	**WPPSI III**	FSIQ 106	VIQ 112	PIQ 100			
9, M	12y 9m	6 m	**WISC III**	FSIQ 84	VIQ 70	PIQ 74			
10, M	3y 1m	12 m	**Leiter-R**	FSIQ 83	Short IQ 87	Reasoning 88			
Time 2									
1, F	7y 5m	18 m	**WISC IV**	FSIQ 119	VCI 102	PRI 119	WMI 115	PSI 126	
3, F	11y 4m	18 m	**WISC IV**	FSIQ 98	VCI 94	PRI 108	WMI 94	PSI 97	
4, F	16y 6m	36 m	**WAIS-R**	FSIQ 103	VIQ 111	PIQ 92			
6, M	17y 5m	12 m	**WAIS-R**	FSIQ 104	VIQ 108	PIQ98			
7, M	3y 6m	12 m	**WPPSI III**	FSIQ 100	VIQ 100	PIQ 100			
8, M	5y 7m	36 m	**WISC IV**	FSIQ 87	VCI 116	PRI 89	WMI 82	PSI 62	
9, M	12y 9m	60 m	**WAIS-R**	FSIQ 98	VIQ 115	PIQ 109			
10, M	3y 1m	36 m	**Leiter-R**	FSIQ 100	short IQ 100	Reasoning 89			
11*, F	13y	31 m	**WISC IV**	FSIQ 99	VCI 86	PRI 100	WMI 79	PSI 109	
12*, F	7y 2m	86 m	**WISC IV**	FSIQ 90	VCI 96	PRI 104	WMI 79	PSI 85	
13*, F	10y	112 m	**WAIS-R**	FSIQ 72	VIQ 76	PIQ 74			

Time 1: first evaluation; time 2: latest evaluation (reported for patients with follow-up longer than 12 months). Grey cells are those with below normal scores

F female, *M* male, *WPPSI-III* Wechsler Preschool and Primary Scale of Intelligence, *WISC-III* Wechsler Intelligence Scale for Children 3rd edn., *WISC-IV* Wechsler Intelligence Scale for Children 4th edn., *WAIS-R* Wechsler Adult Intelligence Scale-Revised, *GMDS 2–8* Griffiths Mental Development Scales 2–8, *Leiter-R* Leiter International Performance Scales-Revised, *FSIQ* Full Scale Intelligence Quotient, *VIQ* Verbal Intelligence Quotient, *PIQ* Performance Intelligence Quotient, *VCI* Verbal Comprehension Index, *PRI* Perceptual Reasoning Index, *WMI* Working Memory Index, *PSI* Processing Speed Index

[a] Patients with first formal evaluation after a median time of 85 months after symptom onset

(patients 3, 4, 6, 9, 10, and 12), in 2 of which (patients 3, and 4) these alternated with episodes of agitation.

All patients had intrathecal synthesis of anti-NMDAR antibodies during the acute phase, with high antibodies titres both in serum and CSF (dilution up to 1:10,000).

At onset, the video-EEG recordings showed slow and non-organized activity in all patients. Diffuse or focal delta-theta activity predominated in the early stages of the disease. Epileptic seizures were reported in 10 patients (patients 1, and 3–11), and video-EEG recorded in 5 (patients 1, 4, 6, 7, and 9).

Brain MRI was normal in 8 patients (patients 2, 4–6, 8, 9, 11, and 12), while 5 patients (patients 1, 3, 7, 10, and 13) showed mild and transient non-specific T2 or FLAIR increased signal abnormalities in different cortical and subcortical regions.

Eleven patients (1–9, 11, and 12) received early first-line immunotherapy consisting of intravenous pulses of methylprednisolone and intravenous immunoglobulin (IVIg) given in combination. This treatment started a median of 3 weeks (range 2–8 weeks) from symptom onset, and was followed by oral steroids tapering over 6 months. No side effects of first-line therapy occurred in any of these patients. An ovarian teratoma was detected in patient 11, 21 months after symptom onset and was removed by unilateral oophorectomy.

Table 2 Serial assessment of language skills, memory, planning, attention and visual-motor integration in patients with anti-NMDAR encephalitis

Patient, sex	Time from symptom onset to assessment	RECEPTIVE AND EXPRESSIVE LANGUAGE SKILLS				MEMORY		PLANNING		ATTENTION			VISUAL-MOTOR INTEGRATION	
		Naming (z)	Verbal Comprehension (z)	Semantic Verbal Fluency (z)	Phonemic Verbal Fluency (z)	Short-Term Verbal Memory (ws)	Short-Term Visuo-Spatial Memory (z)	TOL (z)	BC (ws)	Selective Attention (z)	Sustained Attention (z)	Coding (ws)	VMI (ws.)	ROCF (percentile)
Time 1														
1, F	1 m	-0.7	0.4	-1.3	-1.5	8	NP	-0.1	16	-0.5	-2.4	11	107	30°
2, F	1 m	0.01	-0.16	-2.8	-2	6	-1	-1.2	14	-0.8	-0.2	3	103	10°
3, F	1.5 m	-2.1	-2	-1	-2.7	2	NP	NP	4	-2.4	-1.7	1	68	10°
4, F	2 m	-3	-5	-1.7	-0.1	3	-3.3	-2	4	-2	-2	7	88	<10°
5, F	3 m	-3.6	-2.7	-2.5	1	4	-2	-2.6	3	NP	NP	1	88	<10°
6, M	3 m	-1	-2	-1.7	-1.3	5	0.7	-3.6	4	NP	NP	6	72	<10°
7, M	3 m	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
8, M	6 m	-1	0	-0.6	-0.4	5	-1.2	-3.5	NP	-2	-1.4	NP	89	< 10°
9, M	6 m	-4.2	NP	-1.6	-1.5	8	NP	NP	13	NP	NP	10	NP	25°
10, M	12 m	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
Time 2														
1, F	18 m	0.1	0.7	-0.1	-1.9	11	-0.4	0.05	10	-0.3	0.1	14	94	80°
3, F	18 m	-0.8	1.2	-1.3	-3.9	9	-1	0.3	8	0.3	0.1	11	90	70°
4, F	36 m	NP	NP	0.3	0.3	14	NP	-2	8	NP	NP	8	NP	40°
6, M	12 m	0.4	0.1	-1.3	0.04	13	0.5	-0.6	8	NP	NP	6	88	60°
7, M	12 m	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
8, M	36 m	0.4	1.5	-0.6	-1	5	-2.5	-1	8	-2	-3	3	91	25°
9, M	60 m	-1.8	0	0.3	0.1	11	-0.7	-1.1	13	NP	NP	10	98	40°
10, M	36 m	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
11*, F	31 m	-0.9	0.1	-1	-1.9	6	-2	-2	7	-1	-0.6	6	78	10°-20°
12*, F	86 m	-1.3	-1	-0.6	-0.06	8	-0.4	-0.05	11	-1.3	-1.7	8	83	30°
13*, F	112 m	NP	NP	NP	NP	9	NP	NP	7	NP	NP	7	NP	NP

Time 1: first evaluation; time 2: latest evaluation (reported for patients with follow-up longer than 12 months). Grey cells are those with below normal scores

F female, *M* male, *z* *z*-score in units of standard deviation, *ws* weighted score, *TOL* Tower of London, *BC* block construction, *VMI* visual-motor integration, *ROCF* Rey–Osterrieth Complex Figure Test, *NP* not performed

[a] Patients with first formal evaluation after a median time of 85 months after symptom onset

The two other cases (patients 10, and 13) did not respond well to first-line immunotherapy. Patient 10, who was first treated 6 months from onset, eventually benefited from rituximab. Patient 13 was first diagnosed and treated in 2009 during relapse (mRS score 3) of a condition that had first manifested in 2005.

Disease course

The 11 patients (1–9, 11, and 12) who received early first-line treatment improved a median of 3 weeks (range 2–16 weeks) after starting therapy—a median of 7 weeks (range 4–20 weeks) after symptom onset. Patient 10 started to improve (mRS 3) 12 months after symptom onset, and had recovered well by 24 months (mRS 1). Despite a good response to first-line treatment in 2009, patient 13 experienced a second relapse (mRS score 4) in 2011.

At most recent follow up, 7 patients (patients 1–4, 6, 7, and 9) had no neurological disability (mRS score 0); 5 patients (patients 5, 8, 10–12) had improved substantially (mRS score 1 or 2); behavioural disorders persisted in patient 13 (mRS score 3). All patients had resumed normal life; however in 4 (patients 8, and 11–13) difficulties persisted, mainly evident as poor academic performance and impaired social relationships.

Anti-NMDAR antibodies became undetectable at 1:10 dilution in serum and CSF after a median of 4 months (range 1–20 months) after starting therapy—a median of 5 months (range 2–22 months) after symptom onset.

The EEG pattern progressively normalized after a median of 5 months (range 2–20 months) after starting therapy—a median of 6 months (range 3–24 months) after symptom onset.

At latest follow-up, antibodies were undetectable in serum and CSF, EEG and brain MRI were normal in all patients.

Cognitive/neuropsychological course

Cognition and behaviour were reported normal in all patients before symptom onset. At first clinical observation, severe neurological impairment made formal neuropsychological testing impossible. Following treatment, patients became able to undergo standardized evaluation a median of 3 months (range 1–12) after symptom onset. Tables 1 and 2 show the results of this first assessment (time 1) together with the findings of the latest assessment in patients with follow-up longer than 12 months (time 2).

First evaluation (at time 1)

In patients 1–7 assessment was possible within 3 months (median 2 months, range 1–3); in five of these (patients 3–7) deficits were evident in all explored cognitive/neuropsychological domains, although severity varied. At this stage, only patients 1 and 2 had normal general intellectual abilities, but deficits in verbal fluency, short-term verbal memory, sustained attention and processing speed were found.

Patients 8 and 9 were able to undergo formal neuropsychological assessment 6 months after symptom onset. Both had general intellectual abilities in the normal or lower normal range, but exhibited specific deficits: patient 8, short-term verbal memory, planning, sustained attention and visual-motor integration; patient 9, expressive language and short-term verbal memory.

Patient 10 (unable to speak Italian) became testable 12 months after symptom onset (6 months after starting treatment): Leiter-R testing revealed global cognitive functioning and reasoning in the lower normal range.

Latest evaluation (time 2)

Eight of the 10 patients evaluated at time 1 (patients 1, 3, 4, and 6–10) have a follow-up longer than 12 months. At latest evaluation a median of 27 months (range 12–60 months) after symptom onset, all 8 patients had general intellectual abilities within the normal range, but persisting deficits in phonemic verbal fluency (patients 1, and 3), naming skills (patient 9), working memory and processing speed (patient 8), planning abilities (patients 3, 4, 6, and 8), sustained attention (patients 4, 6, and 8), and short-term verbal and visuo-spatial memory (patient 8).

The three retrospectively recruited patients (patients 11–13) received a single standardized cognitive/neuropsychological assessment 31, 86 and 112 months, respectively, after symptom onset. Patients 11 and 12 had general intellectual abilities at the lower normal range. Patient 11 had difficulties with working memory, phonemic verbal fluency, short-term verbal and visuo-spatial memory, planning, and visual-motor integration; patient 12 was deficient in working memory and processing speed, short-term verbal memory, sustained attention, and visual-motor integration. Patient 13 had general intellectual abilities below the normal range and deficits in planning and sustained attention.

Discussion

NMDARs are known to be crucially involved in learning, memory and cognition in general, via mechanisms that include long-term potentiation and long-term depression [14, 15]. Anti-NMDAR antibodies from patients bind to NMDARs throughout rodent brain but mainly in regions known to have a high density of NMDARs, notably hippocampus and to a lesser extent the frontal cortex [16], where they induce progressive reduction of synaptic and total NMDARs [17]. Reduced NMDAR levels are also observed in the hippocampus of autopsied patients [18]. In parallel with reduction in NMDARs, infusion of patient anti-NMDAR antibodies to rodent brain produces memory and behavioural disturbances, which subside soon after infusion ceases [17]. It is noteworthy that anti-NMDAR antibodies from patients also suppress the induction of long-term potentiation when directly applied to mouse hippocampal slices [19].

Given the role of NMDARs in learning and cognition, it is not surprising that patients experience severe global cognitive dysfunction during the acute phase of anti-NMDAR encephalitis, as reported in all the case series.

In most of our patients, symptoms were so severe soon after disease onset that formal neuropsychological assessment was impossible. For the 10 patients first assessed during the acute phase of their illness, but when the clinical condition had stabilized sufficiently to make formal testing possible, comprehensive cognitive/neuropsychological assessment was possible a median of 3 months (range 1–12) after onset. At this time deficits were found in all domains investigated, although severity varied.

As follow-up progressed (all patients), both general intellectual abilities and neuropsychological characteristics improved progressively, but not uniformly. At most recent assessment, general intellectual abilities were within normal limits in most patients (Table 1), but neuropsychological

deficits were still present in more than half (Table 2), and mainly involved frontal lobe and hippocampal functions (verbal fluency, working memory, executive functions and short-term memory). These persistent deficits typically affected quality of life, social relationships, and academic achievement, although all patients resumed their everyday lives. These findings are closely similar to those reported by Finke et al. [10] in adult patients with anti-NMDAR encephalitis.

That different functions recovered at different rates and extents following treatment is plausibly related to the variable distribution and density of NMDARs within the brain. During the acute phase of the illness, the severe impairment of neurological, cognitive and neuropsychological function suggests widespread cerebral involvement due to disruption of NMDARs throughout the brain by pervasive presence of anti-NMDAR antibodies. As immunotherapy progressively reduced the concentration of anti-NMDAR autoantibodies, improvement would be expected first in functions controlled by brain areas characterised by low NDMAR density. This appears consistent with improved overall disability (mRS score) [20] that in our series occurred a median of 3 weeks after starting treatment in the eleven patients who received early first-line immunotherapy. Nevertheless, the interval between starting therapy and mRS improvement was variable, and required up to 4 months, demonstrating the need to continue treatment in patients who do not respond immediately. The slower or incomplete recovery, in our patients, of general intellectual abilities and neuropsychological functions—which are mainly controlled by the hippocampus and frontal cortex—seems broadly consistent with the fact that the hippocampus and frontal cortex contain the highest density of NMDARs [16, 17]. In the patients in whom formal assessment became possible early, normalization of general intellectual abilities also occurred rapidly. It also appeared that those who recovered rapidly had best recovery of neuropsychological characteristics at most recent assessment (data not shown).

To our knowledge this is the first study to describe cognitive/neuropsychological evolution in children with anti-NMDAR encephalitis: it indicated that although recovery was good in most cases, frontal lobe and hippocampal dysfunctions persisted. However, since it is likely that some patients will continue to improve over time, this conclusion requires confirmation on more paediatric patients followed for a longer period.

We conclude by noting that serial assessment of general intellectual abilities and neuropsychological functions from onset over the long-term is important for detecting specific cognitive impairments in paediatric patients that can be targeted by personalized rehabilitation programmes. Such behavioral and neuropsychological rehabilitation should evolve with the patients as they make gains and should be integrated with medical treatment so as to maximize functional recovery and promote the scholastic and social reintegration of the child.

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Compliance with ethical standards

Conflicts of interest All authors declare they have no conflicts of interest.

Ethical standard For all patients, written consent to be included in the study was obtained from parents or caregivers. The study was conducted in accordance with the Declaration of Helsinki Criteria and was approved by the Ethics Committee of the Foundation IRCCS Neurological Institute C. Besta.

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