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Case study

Anti-N-Methyl-D-aspartate-receptor encephalitis: Cognitive profile in two children

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ABSTRACT

Background: Anti-N-Methyl D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder associated with antibodies against NMDAR resulting in a characteristic neuropsychiatric syndrome characterized by seizures, dyskinesias, and cognitive impairment. The extent and specific tasks associated with cognitive dysfunction in anti-NMDAR encephalitis have not been fully investigated.

Aims: To describe cognitive and neuropsychological profile in two children with anti-NMDAR encephalitis.

Methods: Clinical, laboratory, cognitive and neuropsychological assessments have been performed. Cognitive functions have been evaluated one year after the disease onset, at age 4 years and 10 months in one patient and at age 5 years and 5 months in the other subject. The first patient has been re-assessed one year after the first evaluation.

Results: Both children, who were reported to be normal before disease onset, showed a severe neurological impairment during the acute phase of disease with progressive substantial recovery following treatment. Selective and prolonged attention, activation and integration of semantic information and verbal fluency were particularly impaired. Significant improvements were observed at neuropsychological re-assessment.

Conclusions: Executive dysfunction seems to be the "core" of the neuropsychological profile of children with anti-NMDAR encephalitis. Cognitive abilities may be, at least to some extent, recovered providing that immunomodulatory treatment and specific psychomotor and pedagogical therapy are started soon after disease onset.

1. Introduction

Anti-N-Methyl D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder associated with antibodies against NMDAR resulting in a characteristic neuropsychiatric syndrome clinically represented by seizures, dyskinesias, and cognitive deterioration.[1,2] Although it was initially described mainly in young females with ovarian teratomas, it is relatively frequent in children,[3] often without tumour association. Response to immunomodulatory treatment is usually good,

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but relapses may occur.[3,4,7] Cognitive impairment is almost invariably reported but the extent and specific tasks associated with cognitive dysfunction in anti-NMDAR encephalitis have not been fully investigated.

We report here the cognitive profile of two children with anti-NMDAR encephalitis who underwent a comprehensive neuropsychological assessment around one year and two years respectively after having recovered from the active stage of the disease.

2. Case reports

Case 1 is a girl with NMDAR-antibodies firstly depicted at 4 years, whose clinical, neuroradiological and laboratory findings have been previously reported.[5] She had no tumour and has been followed-up for two years, showing a progressive clinical improvement, on low-dose steroids daily and IVIG cycles every 40 days, in association with specific psychomotor and pedagogical therapies. Serum NMDAR-antibodies have been re-assessed during follow-up showing a significant reduction but remaining just detectable (at 1:20 dilution) in serum at the last evaluation two years after diagnosis. At age 4 years and 10 months, i.e. around ten months after the disease onset, cognitive and neuropsychological evaluations were performed, with re-assessment one year later (See below).

Case 2 is a boy of 3 years and 8 months who was brought to the emergency department of the local hospital with a generalized seizure in 2008. Around five days before, right lower limb dystonic-like movements were observed by the parents. CT scan was normal. Electroencephalography (EEG) showed slow spike and waves. Soon after admission, he started to show progressive difficulties in walking and in speech. Despite therapy (acyclovir, antibiotics, steroids, carbamazepine, haloperidol, biperidene and diazepam) his neurologic condition worsened over the following days and he developed mood changes, irritability, fluctuation in consciousness, expressive dysphasia, upper limb dyskinesias, and he finally lost the ability to walk. Some episodes of autonomic instability (labile blood pressure, bradycardia/tachycardia, and diaphoresis) occurred. Two months after the symptom onset, he was admitted to our Unit. The neurological examination showed poor social interaction, absence of speech, orofacial dyskinesias, left upper arm dystonia and inability to walk. Thyroid-stimulating hormone, fT3, fT4, antithyroglobulin and anti-thyroid peroxidase antibodies, and urine organic acid values were normal. Serum immunoglobulin M for human herpes virus 6, adenovirus, rubella, measles, mumps, herpes virus 1-2, chickenpox, cytomegalovirus, Epstein Barr virus, Borrelia, and parvovirus B19 were negative. Blood and cerebrospinal fluid (CSF) polymerase chain reactions for DNA of adenovirus, cytomegalovirus, Epstein Barr virus, human herpes virus 6, herpes simplex virus-1 and -2, parvovirus B19, and Mycoplasma pneumoniae were negative. Unmatched oligoclonal bands were present in CSF. The brain and spinal cord MRI were normal. The EEG showed slow background activity and bilateral high voltage slow and sharp waves. Brainstem auditory evoked potentials and somatosensory evoked potentials were normal.

With the presumptive diagnosis of autoimmune encephalopathy, intravenous immunoglobulin (IVIG; 400 mg/kg for 5 days) was administered once and oral prednisone (1.5 mg/kg/d) was continued for three months. Other drugs were gradually discontinued. He showed a rapid improvement of motor skills, being able to walk independently and pronounce many words and sentences soon after the IVIG cycle. However, he still showed inability to concentrate and complete simple tasks, hyperactivity, limited interest in social interaction, and difficulty in verbal comprehension. During the following months he was followed-up at the same hospital in which he was firstly admitted, showing a slowly progressive improvement of cognitive and behavioural functions.

More than one year after the onset of symptoms, on the basis of the literature and of the clinical experience of Case 1, diagnostic suspicion of anti-NMDAR encephalitis was suggested. The antibodies, detected as described previously,[7] were positive in serum (score 4 (range 0–4, nv $<$ 1) at 1:20 and 4 at 1:400) and in CSF (score 3 at 1:2 and 1 at 1:20) stored from the time of first admission to our Hospital. Voltage-gated potassium channel and anti-glutamic acid decarboxylase antibodies were negative. To rule out the presence of an occult tumour, we performed abdominal and pelvic ultrasonography, whole body MRI, and guanidine scintigraphy, which showed no abnormalities. No further immunotherapies were given. At age 5 years and 5 months, neurological examination was normal and serum NMDAR-antibodies were substantially reduced (just detectable at 1:400) The results of cognitive and neuropsychological evaluation are summarised below.

3. Cognitive and neuropsychological assessment

The cognitive assessment included the Griffiths Mental Development Scale-Extended Revised (GMDS-R) and a comprehensive neuropsychological protocol including different tests. The results of the cognitive and neuropsychological assessments are summarised in Table 1. The general quotient (GQ) was 85 in patient 1 and 65 in patient 2, respectively. The results of the different neuropsychological tests were grouped into five cognitive domains, as indicated in Table 1, to illustrate the pattern of cognitive function. The neuropsychological assessment showed significant deficits in selective and prolonged attention, in problem-solving tasks and thinking flexibility, and in verbal fluency (with many intrusions and perseverations at switching and clustering semantic tasks, and significant deficit in the rapid naming test). Both patients showed adaptive behaviour changes, with control behaviour deficiency in the cognitive, social and emotional domains.

The neuropsychological re-assessment performed one year later in pt.#1 showed normalization of the GQ (96) with significant improvements in the selective/prolonged attention and problem-solving tasks and normal results in both switching and clustering semantic tasks.

4. Discussion

In children with anti-NMDAR encephalitis, behavioural changes such as temper tantrums, hyperactivity, or irritability

Table 1 – Cognitive and neuropsychological assessments.

Function	Test[a]	Pt1	Pt2	Age range and test description
cognitive	**GMDS-ER** (Griffiths R. Griffiths Mental Development Scale-Extended Revised. Organizzazioni Speciali: Firenze, 2006) **Total Scale GQ**	−1.9	−2.3	2–8 years Mental Development
	Subscale A: Locomotor	−1.5	−2	
	Subscale B: Personal-Social	−1.5	−1.7	
	Subscale C: Language	−2	−2.3	
	Subscale D: Eye and Hand Co-ordination	−1.4	−2.3	
	Subscale E: Performance	0.9	−2.3	
	Subscale F: Practical Reasoning	−1.5	−1.9	
visual and verbal memory	**Digit span Forward** (Orsini et al. Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. It J Neurol Sci 1987; 8: 539–48)	−0.5	0	4 years to adulthood, verbal short term memory
	Corsi's Blok tapping test forward (Orsini et al. Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. It J Neurol Sci 1987; 8: 539–48)	−1.9	−3	4 years to adulthood, visuo-spatial short term memory
	Luria memory words test (Bisiacchi P et al. BVN 5–11. Batteria di valutazione neuropsicologica per l'età evolutiva. Erickson: Trento, 2005)	9°P 25°P	16°P 37°P	5–11 years, memory words test:learning and delay recall
attention	**Bell Test** (Biancardi A, Stoppa E. Il test delle Campanelle modificato: una proposta per lo studio dell'attenzione in età evolutiva. Psichiatria dell'Infanzia e dell'Adolescenza 1997; 64: 73-84)	−2 −3	−3.9 −4.6	4–14 years, selective and prolonged attention
executive functions	**Tower of London** (Sannio Fancello G et al. TOL: Torre di Londra. Erickson: Trento, 2007)	−2.3	−4	4–13 years, problem-solving tasks
language functioning (receptive and expressive)	**T.R.O.G.** Test for reception of grammar (Bisiacchi P et al. BVN 5–11. Batteria di valutazione neuropsicologica per l'età evolutiva. Erickson: Trento, 2005)	−2	−2	5–11 years, comprehension of increasing complexity orders
	Peabody Picture Vocabulary Test (Stella G et al. OMEGA: Torino, 2000)	5°P	12°P	2–17 years, receptive vocabulary
	Naming Test (Bisiacchi P et al. BVN 5–11. Batteria di valutazione neuropsicologica per l'età evolutiva. Erickson: Trento, 2005)	−3	−3	5–11 years, expressive vocabulary
	Fluency (Bisiacchi P et al. BVN 5–11. Batteria di valutazione neuropsicologica per l'età evolutiva. Erickson: Trento, 2005)	−2	−2	5–11 years, semantic fluency
visual-motor integration	**Developmental Test of Visual- Motor Integration** (VMI/Beery – Buktenika) (Beery KE. VMI. Organizzazioni Speciali: Firenze; 2000)			3–17.11 years, development of visual-motor integration
	Copying form test	16°P	2°P	
	Visual perception test	21° P	0.6°P	
	Motor coordination test	10° P	0.6°P	

The bold text indicates the name of the different tests.
a Performances in each test were converted in z-scores (i.e. is a statistical measure that quantifies the original score in terms of the number of standard deviations that that score is from the mean of the distribution) or percentiles using normative data reported in the literature and data from healthy populations obtained in current clinical practice using normal procedures. GQ: general quotient.

and language disintegration with severe speech reduction up to frank mutism are usually reported as early features of the disorder.[2,3,5–7] Memory loss may be difficult to evaluate due to behavioural changes and speech problems. To the best of our knowledge, detailed neuropsychological investigations at recovery have not been described in the literature either in adults or in children.

We were able to identify a neuropsychological profile consistent with executive dysfunction in both patients, with particular impairment of selective and prolonged attention, activation and integration of semantic information and verbal fluency. Gestalt visuoperceptive abilities were relatively preserved in both patients and spatial visuoconstructive abilities were relatively preserved in patient #1. Although premorbid evaluations are not available, both children were reported to be normal before the acute onset of encephalitis that occurred at a very similar age in both of them (4 years and 3 years and 8 months, respectively). Interestingly, we observed a re-normalization of the global quotient in pt.#1, one year after the first evaluation and twenty-two months from onset, indicating that despite the severity of the neuropsychiatric impairment in the acute stage of the disease, cognitive dysfunction is transient and an apparent full recovery is possible. Further cognitive evaluation will be scheduled to evaluate the real entity of the recovery. It is possible that the association of the immunomodulatory treatment and the specific psychomotor and pedagogical therapy contributed to this outcome. On the other hand, a mild mental retardation, as assessed two years after the disease onset, was found in patient 2 who underwent immunomodulatory treatment for three months only, because of lack of awareness of the diagnosis at that time. Although neurologically normal, it is possible that there are still antibodies in serum or CSF that might be impairing cognitive

functions in both these patients and only time will tell the full extent of recovery.

These data are in line with the demonstration that patients' antibodies cause a selective and reversible decrease in NMDAR surface density and synaptic localization that deregulates the glutamatergic pathways.[2] NMDAR are glutamate-gated ion channels involved in the regulation of synaptic function in the central nervous system and implicated in many fundamental functions, including neuronal plasticity, neurotoxicity, learning, and memory.[8]

In animal models it has been demonstrated that the noncompetitive, highly specific NMDAR antagonist dizocilpine (MK-801), may induce dose-dependent impairment of learning and memory.[9] Furthermore, other noncompetitive NMDAR antagonists such as phencyclidine and ketamine induce psychotic symptoms and cognitive disturbances, namely deficits in pre-attentive information processing, in healthy individuals. In particular, the schizophrenia-like effects of NMDAR antagonists have been related to changes in the NMDAR signalling involved the prefrontal cortex.[10] The prefrontal cortex and frontostriatal structures are critical for executive functions, i.e. the different regulatory cognitive abilities that include sustaining attention and shifting/dividing attention in a task-appropriate manner, regulating behaviour and emotion, allowing to plan correctly how to achieve goals and organizing behaviours and thoughts. As described in the literature and analysed in detail in our study, the neuropsychiatric features of anti-NMDAR encephalitis, are consistent with impairment of subcortical structures, limbic regions, amygdalae, and frontostriatal circuitry.[2,7,8,10]

Finally, it has been recently reported that mutations in two genes (*GRIN2A* and *GRIN2B*) encoding either the NR2A or the NR2B subunits of the NMDAR may cause variable degree of cognitive impairment ranging from learning disabilities to severe mental retardation variably associated with behavioural changes and epilepsy.[11] Thus, the essential role of NMDAR during the development of neurocognitive function, namely of learning and memory has been further demonstrated.

In conclusion, our study showed that executive dysfunction is the "core" of the neuropsychological profile of children with anti-NMDAR encephalitis. Cognitive abilities may be, at least to some extent, recovered providing that immunomodulatory treatment and specific psychomotor and pedagogical therapy are started soon after disease onset. Further studies are needed especially to evaluate the long-term cognitive outcome in children with this immune-mediated disorder.

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