Published in final edited form as:
J Neurol. 2010 October ; 257(10): 1686–1691. doi:10.1007/s00415-010-5604-6.

Reversible brain atrophy in anti-NMDA receptor encephalitis: a long-term observational study

Takahiro Iizuka,
Department of Neurology, School of Medicine, Kitasato University, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan

Shintaro Yoshii,
Department of Neurology, School of Medicine, Kitasato University, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan

Shinichi Kan,
Department of Radiology, School of Medicine, Kitasato University, Sagamihara, Kanagawa, Japan

Junichi Hamada,
Department of Neurology, School of Medicine, Kitasato University, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan

Josep Dalmau,
Division of Neuro-oncology, Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA

Fumihiko Sakai, and
International Headache Center, Shinyurigaoka, Kanagawa, Japan

Hideki Mochizuki
Department of Neurology, School of Medicine, Kitasato University, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan

Takahiro Iizuka: takahiro@med.kitasato-u.ac.jp; Shintaro Yoshii: yoshii@med.kitasato-u.ac.jp; Shinichi Kan: shkan@kitasato-u.ac.jp; Junichi Hamada: jhamada@med.kitasato-u.ac.jp; Josep Dalmau: Josep.Dalmau@uphs.upenn.edu; Fumihiko Sakai: fsakai@mist.dti.ne.jp; Hideki Mochizuki: hmoc0823@med.kitasato-u.ac.jp

Abstract

The long-term neuroimaging correlates of clinical recovery have not been described in anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis. The aim of the study is to evaluate the long-term outcome of brain atrophy in anti-NMDAR encephalitis. Patients were two women (ages 17 and 33 years) with severe anti-NMDAR encephalitis resulting in decreased level of consciousness, autonomic instability, hypoventilation, and dyskinesias requiring continuous infusion of anesthetic agents for 6–7 months. Brain MRI and cerebral blood flow SPECT obtained at the time of maximal neurological disability were compared with similar studies obtained 5–7 years later. Both patients were hospitalized for 9–14 months and developed frontotemporal atrophy and

Correspondence to: Takahiro Iizuka, takahiro@med.kitasato-u.ac.jp.

This study was originally presented at the scientific session of the 61th Annual Meeting of American Academy of Neurology on 21 April 2009.

Conflict of interest statement The authors have nothing to disclose regarding conflicts of interest or commercial relationships including grants, honoraria, speaker's lists, significant ownership, or financial support from pharmaceutical or other companies.

hypoperfusion 7–12 months after symptom presentation. In both patients, cognitive functions gradually improved over the next 4–5 years. Comparative neuroimaging studies obtained 5–7 years after symptom presentation showed dramatic improvement of the atrophy and frontotemporal hypoperfusion. The severe and protracted deficits and the frontotemporal atrophy that occur in some patients with anti-NMDAR encephalitis are potentially reversible. This suggests that a functional rather than a structural neuronal damage underlies the pathogenesis of this disorder.

Keywords

Paraneoplastic; Encephalitis; Brain atrophy; NMDA receptor; MRI

Introduction

Anti-*N*-methyl-D-aspartate (aspartic acid) receptor (NMDAR) encephalitis is a disorder likely mediated by antibodies against the NR1 subunit of the NMDAR and characterized by rapidly progressive psychiatric symptoms, seizures, unresponsive/catatonic state, dyskinesias, and autonomic instability [1–3]. The disorder was originally described as a paraneoplastic syndrome associated with ovarian teratoma [1], but it has become clear that a substantial number of patients do not have tumors and that men and children are also affected [3]. When it is found to be paraneoplastic, early tumor resection along with immunotherapy is recommended [3] although spontaneous prolonged recoveries have been reported [2]. The long-term neuroimaging correlates of clinical recovery have not been described. We report here comparative neuroimaging studies of two patients followed for 5–7 years.

Patients and methods

We previously reported a long-term functional outcome of four patients with anti-NMDAR encephalitis who did not have surgical resection of the associated tumor [2]. Two of the patients (original case number #1 and #2) spontaneously recovered without development of brain atrophy, but the other two patients (case number #3 and #4) developed brain atrophy during the course of the disease. Despite the presence of brain atrophy, these two patients gradually recovered over 3–4 years. We performed a long-term follow-up neuroimaging study of the last two patients who developed a long-lasting decreased level of consciousness, dyskinesias, autonomic instability, and hypoventilation [2]. Anti-NMDAR antibodies were detected in archived serum and CSF obtained during the acute stage of the disease, but not in serum obtained 4–6 years after the patients' recovery. We briefly summarize the patients and describe in detail the treatments given during hospitalization and the outcome after a long-term follow-up.

Both patients presented with psychiatric symptoms following a prodromal cold-like syndrome, and progressed during the next 8–13 days to an unresponsive, catatonic-like state. Patient #1 (a 17-year-old girl) had a tonic seizure at the peak of symptoms of psychosis, while patient #2 (a 33-year-old woman) had no seizures. At admission, both patients were mute, unresponsive to verbal commands, and gradually developed involuntary movements predominantly involving orofacial muscles that lasted for 12 months (patient #1) and 6 months (patient #2). Patient #1 required mechanical ventilation for 9 months, and patient #2 for 6 months. Both patients received intravenous administration of acyclovir, immunoglobulin (0.4 g/kg/day, 5 days) and high-dose methylprednisolone (1,000 mg/day, 3 days, two courses) without beneficial effect. The orofacial dyskinesias did not respond to

conventional doses of antiepileptic agents, thus a long-lasting continuous infusion of anesthetic agents for 6–7 months was required to suppress the dyskinesias.

In patient #1 the antiepileptic agents sequentially used included, carbamazepine (600 mg/day, 22 days), valproate (800–1,200 mg/day, 16 days), zonisamide (300 mg/day, 8 days), clobazam (10–30 mg/day, 5 months), clonazepam (1.5–3.0 mg/day, 9 months), and intravenous phenytoin. However, none of these agents was effective for the dyskinesias. She also received an intravenous infusion of propofol (0.40–3.92 mg/kg/h, 7 months) with an additional infusion of thiopental (1.29–3.61 mg/kg/h, 20 days) or midazolam (0.03–0.18 mg/kg/h, 6 days), but these agents were only effective at high dosage. Thus, the involuntary movements persisted for 12 months. The clinical course was complicated by systemic infections, septic shock, deep vein thrombosis, disseminated intravascular coagulation, and arterial thrombosis leading to leg amputation. Fourteen months after admission, she was discharged to a nursing home in an apparent vegetative state; she remained on clonazepam (3.0 mg/day) until it was discontinued 5 years later. Patient #2 was put on various combinations of antiepileptic agents, including carbamazepine (400–600 mg/day, 2 months), clonazepam (1.5–6 mg/day, 5 months), phenytoin (300 mg/day, 1 month), valproate (800–1,200 mg/day, 15 days), phenobarbital (50–100 mg/day, 3 months), clobazam (10–40 mg/day, 9 months) and zonisamide (300–600 mg/day, 7 months). She also received an intravenous infusion of midazolam (0.06–1.28 mg/kg/h, 5 months) and propofol (0.43–4.57 mg/kg/h, 6 months). She was unresponsive for the first 7 months, but afterwards she began to follow simple commands, and 9 months after admission she was transferred to a rehabilitation center. She remained on clobazam (30 mg/day) and zonisamide (300 mg/day) until they were discontinued 4 years later.

MRI and SPECT studies

Brain MRI and cerebral blood flow (CBF) SPECT obtained at the time of maximal neurological disability (7–12 months after symptom onset) were compared with similar studies obtained 5–7 years later (after recovering from the disorder). Serial MRI studies were not intended to measure the cerebral volume, and the long-term follow-up did not allow us to use the same MRI equipment or use a voxel-based morphometric analysis. Therefore, visual analysis was used to assess chronological changes in cerebral volume.

For SPECT study, *N*-isopropyl[123I]-*p*-iodoamphet-amine was used as a flow tracer. Both hyperperfusion and hypoperfusion images were created using three-dimensional stereotactic surface projection (3D-SSP) analysis (Z-score mapping) as previously reported elsewhere [4]. CBF was assessed based on 3D-SSP hypoperfusion images.

Cognitive function was evaluated using a Revised Hasegawa Dementia Scale (HDS-R) that is equivalent to the mini-mental state examination.

Results

Patient #1

This patient remained in an apallic state for 6 months after discharge. Two years after presentation she began to talk and follow simple commands. Three years after presentation the HDS-R was 27/30, and 1 year later she was able to talk without difficulty. Five years after presentation the cognitive functions had returned close to baseline with HDS-R score of 30/30, and dysgraphia in Kanji. At the last follow-up, 9 years after symptom presentation, the patient had no evidence of teratoma. No relapsing symptoms of encephalitis occurred during this 9-year period.

Serial brain MRI revealed progressive atrophy predominantly in the medial temporal lobes, which was most prominent 7–11 months after admission (Fig. 1b), but approximately 7 years later a dramatic improvement was seen (Fig. 1c). SPECT obtained 12 months after presentation, when she remained unresponsive even 5 months after discontinuation of anesthetic agents, showed mediofrontal and temporal hypoperfusion (Fig. 1d), but 6 years 9 months later hypoperfusion was less marked (Fig. 1e).

Patient #2

After discharge this patient continued to improve cognitively and physically. Three years later, she went back to work. Four years after symptom presentation the HDS-R score was 30/30. By that time an MRI of the pelvis demonstrated a right ovarian tumor that was removed, with pathological diagnosis of mature teratoma [2]. She has been followed 7 years without evidence of relapsing encephalitis.

Neuroimaging studies obtained 7–8 months after symptom presentation reveled mild frontotemporal atrophy (Fig. 2b) and prefrontal and mediofrontal hypoperfusion (Fig. 2d). Repeat studies 5 years later showed a dramatic improvement in both cerebral volume and CBF (Fig. 2c, e). Mild cerebellar atrophy and cerebellar hypoperfusion were seen in the follow-up study, without clinical signs of cerebellar dysfunction.

Discussion

This study shows that, in patients with anti-NMDAR encephalitis, the development of brain atrophy in the context of severe and protracted symptoms does not necessarily indicate a poor clinical outcome.

The mechanism of reversible brain atrophy remains unknown. It has been reported in a few toxic, metabolic, or nutritional disorders such as chronic alcoholism [5], Cushing syndrome [6], anorexia and bulimia nervosa [7], chronic fatigue syndrome [8], and in association with the use of corticosteroids [9] or valproate [10], but it has not been reported in encephalitis.

Our patients received high-dose intravenous methylprednisolone during the acute stage of the disease. High-dose corticosteroids may induce reversible short-term loss of volume [9], but the brain atrophy of our patients was not short-lasting. Chronic low doses of corticosteroids may also contribute to irreversible loss of tissue through steroid-induced protein catabolism [9], however, our patients were not chronically treated with corticosteroids. Although both patients received valproate, this was used for a short period of time (less than 16 days) making a possible role for the atrophy unlikely. It is unknown whether prolonged use of anesthetic agents causes brain atrophy or not, but it is possible that continuous neuronal suppression with GABAergic agents may contribute to loss of volume without loss of axons or neurons by altering tissue metabolisms, protein synthesis and intracellular water balance.

We postulate that the NMDAR immune response contributed to the brain atrophy of our patients. The predominant clinical and radiological involvement of the frontotemporal regions, where NMDAR are present at high density, suggests an immunological cause of the atrophy. Indeed, studies show that antibodies cause internalization of synaptic receptors and a decrease of NMDAR-mediated currents [11], likely resulting in functional disruption of neuron–astrocyte networks and alteration of tissue metabolisms, particularly in the frontotemporal lobes, contributing to hypoperfusion and loss of volume in these areas.

Reversibility of both brain atrophy and cognitive dysfunction suggests the presence of a distinctive pathophysiology in this disorder. This is in contrast with classic paraneoplastic

encephalitis with antibodies to intracellular antigens, in which cytotoxic T cell mechanisms are likely involved, and are usually associated with progressive and irreversible brain atrophy and neurological deficits. In our patients, no parenchymal lesions were noted in the MRI except for a subtle, transient increase of FLAIR signal in the medial temporal lobes of patient #1 [2]. Previous autopsy studies demonstrated deposits of IgG and microgliosis, but absence of complement, rare T cell infiltrates, and absent or very rare neurons undergoing neuronophagia [1,12]. Relative preservation of neurons may contribute to subsequent recovery of brain volume as well as functional recovery.

Although we cannot exclude a potential pharmacological effect on neurons or astrocytes by anesthetic agents, the gradual functional recovery of the patients could be related to synaptic plasticity or remodeling of neuron–astrocyte–vascular networks after the immune-mediated synaptic disruption. Results of this study should provide hope to families of patients with this disorder indicating the need of prolonged clinical, behavioral, and cognitive rehabilitation.

Acknowledgments

We are extremely grateful to all participants for their contribution to this study, and acknowledge the efforts of all research staffs who worked on the clinical and neuroimaging data collection.

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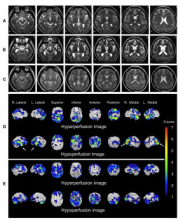

Fig. 1. T2-weighted MRI and SPECT of patient #1

a MRI on admission is normal. **b** MRI obtained 7 months later shows marked frontotemporal atrophy. **c** Follow-up MRI obtained 7 years 6 months after presentation shows marked improvement of atrophy. **d** SPECT obtained 12 months after admission shows mediofrontal and temporal hypoperfusion. **e** Follow-up studies obtained 7 years 9 months after presentation demonstrate improvement of hypoperfusion. *Arrows* indicate hypoperfusion

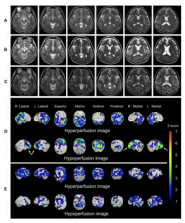

Fig. 2. T2-weighted MRI and SPECT of Patient #2

a MRI is normal on admission. **b** MRI obtained 8 months later shows moderate frontotemporal atrophy. **c** Follow-up MRI obtained 5 years 10 months after presentation shows improvement of atrophy. **d** SPECT obtained 7 months after admission shows prefrontal and mediofrontal hypoperfusion. **e** Follow-up SPECT obtained 5 years 10 months after presentation shows improvement of initial hypoperfusion. *Arrows* indicate hypoperfusion