will provide the patient with the most successful surgical and functional outcome.

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Recovery from severe frontotemporal dysfunction at 3 years after N-methyl-D-aspartic acid (NMDA) receptor antibody encephalitis

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ABSTRACT

Encephalitis associated with antibodies against N-methyl-D-aspartic acid (NMDA) receptor is characterized by severe memory deficits, decreased consciousness, epileptic seizures and movement disorders and occurs most commonly in young women. Recovery is mostly good but little is known about the disease course in patients whose treatment has been delayed severely. We present a 16-year-old girl with a 36-month follow-up. A single course of methylprednisolone attenuated some symptoms but severe and incapacitating frontotemporal syndrome remained. Second-line treatment with rituximab was initiated 12 months after the onset of symptoms. A surprising recovery occurred 18 months after treatment and 30 months after onset. Recovery in NMDA receptor antibody-associated encephalitis can be severely delayed and does not have to be linear. Whether delayed therapy contributed to recovery in this patient cannot be answered with certainty. Spontaneous recovery independent of therapy is possible, as it has been observed previously as late as 3 years after onset. Although serum antibodies disappeared with recovery in this patient, previous cases have shown serum antibodies to be unreliable markers of disease activity. Second-line treatment, especially with substances as well tolerated as rituximab, should at least be considered in NMDA receptor encephalitis with persistent neuropsychiatric syndromes after first-line therapy.

1. Introduction

Encephalitis associated with antibodies against N-methyl-D-aspartic acid (NMDA) receptor is characterized by severe memory deficits, decreased level of consciousness, epileptic seizures, autonomic dysfunction and movement disorders and occurs most commonly in young women, often with ovarian teratoma. Recovery is mostly good but severe residual neuropsychological dysfunction and fatalities are known. Little is known about the disease course after treatment has been delayed severely.[1]

2. Case report

We report a 16-year-old girl who was diagnosed and treated for NMDA receptor encephalitis more than 1 year after disease manifestation. In August 2008, the patient suffered four generalized tonic-clonic epileptic seizures over 2 weeks. Personality changes, restlessness, sensory aphasia, memory and attentional deficits, anxiety, hallucinations, abulia and eventually fluctuating catatonia developed over 2 more weeks. A cerebral MRI 1 week after the first seizure showed nonspecific left frontal and right temporal subcortical T2-weighted hyperintensities without gadolinium enhancement. Electroencephalography demonstrated right temporal slowing and epileptic discharges and cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis. After exclusion of herpes simplex encephalitis, autoimmune encephalitis was diagnosed and a single course of intravenous (IV) methylprednisolone (1 g/day) for 5 days was commenced. Catatonia improved, MRI changes receded and the CSF cell count normalized but previously undetectable oligoclonal bands were detected (4 months after onset). However, a severe neuropsychiatric syndrome with hyperphagia, hypersexuality, severe attentional deficits, marked disorder of impulse control and personality changes with aggressive behavior remained despite neuroleptic pharmacotherapy (risperidone, pipamperone, quetiapine, chlorprothixen, haloperidone, levomepromazine). In June 2009, 10 months after disease onset, positive NMDA receptor immunoglobulin G (IgG) antibodies were detected in serum (titer 1:320, indirect immunofluorescence using NMDA receptor subunit NR1 transfected HEK293 cells).[2]

The patient was transferred to the University Medical Center Hamburg Eppendorf. On examination, severe frontotemporal lobe dysfunction was observed. She was severely inattentive, child-like,

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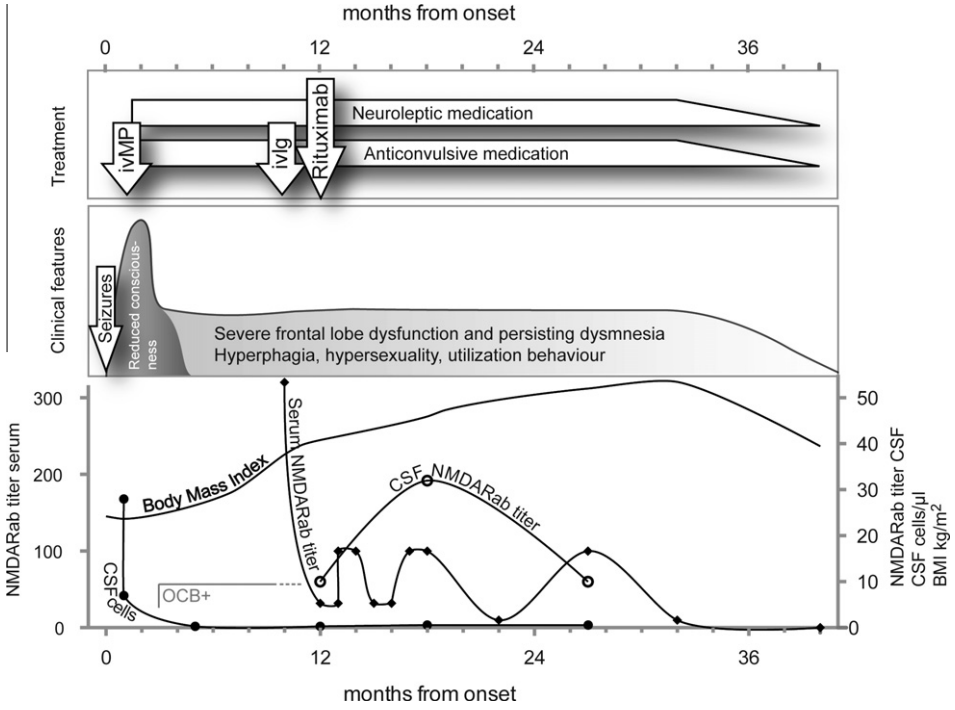

Fig. 1. Schematics of clinical course, treatment and N-methyl-D-aspartic acid receptor (NMDAR) antibody titers. ivMP = intravenous methylprednisolone (5 × 1 g), ivIG = intravenous human immunoglobulin (150 g over 5 days), rituximab (2 × 1000 mg/day, day 1 and day 15). Body mass index (BMI), cerebrospinal fluid (CSF) cells and CSF NMDAR antibody titer on the right y-axis, serum NMDAR antibody titer on the left y-axis. Clinical features are reported as clinical impression and information from parents. (For neuroleptic and anticonvulsive medication, see main text.)

constantly fidgeting, situationally and temporally disoriented, completely unstable emotionally with fast changes between cheerful, aggressive and depressed, as well as completely uncooperative. Severe short-term and long-term memory deficits were observable. Oculomotor apraxia and difficulty with externally initiated saccades, as well as disturbed suppression of anticipatory saccades, was noticed. Generalized but slight chorea was present. She was obese (body mass index BMI 38 kg/m^2), constantly preoccupied with food, exhibiting hyperoral, hypersexual and utilization behavior. Medication consisted of valproate (2400 mg), risperidone (4 mg), levomepromazine (140 mg) and biperidene (4 mg).

Cerebral MRI showed nonspecific subcortical T2-weighted abnormalities that were identical to earlier imaging. The CSF analysis demonstrated normal cell counts but isolated oligoclonal IgG. Transvaginal ultrasound and whole body fluor-deoxyglucose positron emission tomography did not reveal any underlying ovarian or extra-gonadal tumors. She was treated by IV Ig infusion (150 g) 10 months after onset. The syndrome did not improve. Finally, she was treated with rituximab 2 × 1000 mg/day (days 1 and 15) 12 months after onset. Although systemic B-cells (CD19 cells) remained undetectable for 12 months after treatment, serum titers of NMDA receptor antibody remained detectable and fluctuated between 1:100 and 1:32, CSF titers between 1:10 and 1:32 over the next 1.5 years (Fig. 1). Frontal dysfunction and memory deficits remained unaltered, and despite discontinuing risperidone and switching to olanzapine, her weight continued to increase. She was constantly treated as an in-patient in child psychiatry and rehabilitative units over the ensuing months. She was eventually discharged from rehabilitation without significant improvement in January 2011, 2.5 years after disease onset.

Surprisingly over the next 6 months and without preceding changes of the pharmacological regime, the frontal dysfunction and memory deficits improved rapidly. Neuroleptic and anticonvulsive medication could be slowly tapered. Subsequently, 3.2 years after disease onset, only subclinical difficulty on suppression of anticipatory saccades and Stroop paradigm remained.[3] Memory, orientation, impulse control and emotional stability recovered completely. Serum NMDA receptor antibodies were no longer detectable (Fig. 1). No tumor has been found. She is being reintegrated into school, currently visiting a school for children with learning difficulties but performing within the top 20% of her class. She is successfully working on weight reduction, which is continuously decreasing (Fig. 1).

3. Discussion

We describe an adolescent girl with typical idiopathic NMDA receptor antibody-associated encephalitis. The clinical presentation with epileptic seizures, memory and attentional deficits and catatonia with CSF pleocytosis and nonspecific changes on MRI is typical of this newly recognized entity. However, the condition was initially not detected and treated with only a single dose of IV steroids 1 month after onset. Although some improvement was observed, a severe residual frontal and temporal dysfunction remained. Second-line therapy with IV Ig and rituximab was instituted 12 months after onset. However, improvement did not commence until 30 months after onset. Recovery 3 years after onset is now almost complete and full recovery is anticipated.

This report illustrates that recovery from NMDA receptor encephalitis can be very delayed and does not have to be linear. Recovery should not be ruled out even years after disease onset and great caution communicating a negative prognosis is advisable. Whether second-line therapy contributed to delayed recovery cannot be answered with certainty. The 18-month interval between rituximab and recovery is fairly long; however, not much is known about the dynamics of the disease in delayed treatment settings. Spontaneous recovery independent of therapy is possible,

as it has been observed as late as 3 years after onset.[4] Although serum antibodies disappeared with recovery in this patient, previous reports have shown serum antibodies to be unreliable markers of disease activity.[5] Nevertheless, until reliable markers are established, second-line treatment, especially with substances as well tolerated as rituximab, at least should be considered in persistent neuropsychiatric syndromes.

Conflicts of interest/disclosures

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Symptomatic progression of degenerative scoliosis after decompression and limited fusion surgery for lumbar spinal stenosis

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ABSTRACT

Significant degenerative scoliosis together with lumbar spinal stenosis increases the complexity of planning a surgical intervention for iatrogenic instability may be introduced by decompression in the midst of the curve, especially at or near the curve apex, that may lead to more rapid progression of a deformity, especially if surgery is at, or is near, the apex of the curve and a listhesis is present. Surgical options include simple laminectomy, a laminectomy with limited fusion, or an extensive fusion that addresses the overall curve, but there is no consensus as to the best approach. There is scant information in the literature about specific instances of failure of a limited surgical approach from which any instructive lessons may be learned. We report a surgical failure in a 59-year-old woman with degenerative lumbar stenosis and scoliosis from L3–5 and L3–4 disc herniation treated with a simple hemilaminectomy and discectomy, a subsequent fusion for symptomatic progression of deformity, and a third surgery to fuse the entire scoliotic curve after development of severe deformity, pain, and neurological deficits. We conclude that surgical decision-making should take into consideration any risk factors for deformity progression as well as overall sagittal and coronal balance and advise that similar patients be followed for a lengthy period following surgery to monitor for stability.

1. Introduction

Lumbar spinal stenosis (LSS) is a major cause of pain and disability that is increasing in frequency with the aging population. Coincident degenerative lumbar scoliosis (DLS) increases the complexity of surgical planning: decompression within the curve may introduce iatrogenic instability and progression of deformity, especially at or near the apex of a curve or a listhesis[1,2] There is no consensus if optimal surgical management should be simple decompression, short-segment fusion, or extensive surgery addressing the overall curve. Discourse about this clinical problem is limited by lack of information about the incidence of deformity progression following decompressive surgery; moreover, the literature contains few examples of treatment failure from which instructive lessons can be learned.[4] We present a patient with LSS with DLS wherein symptomatic progression of deformity occurred following simple decompression and a subsequent short-segment fusion.

2. Case report

A 59-year-old woman complained of worsening low back and right leg pain unresponsive to epidural steroid injection (ESI) and physical therapy. Neurologic examination demonstrated right L4 dermatomal sensory loss and a diminished right knee jerk. Imaging studies (Fig. 1) showed L3–5 LSS, mild DLS, and disc extrusion at

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