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Case Report

Probable Antibody-Negative Autoimmune Encephalitis in a Fifteen-Year-Old Girl with Previous Surgery for a Low-Grade Brain Tumor

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Abstract

A fifteen-year-old girl presented with symptoms of encephalitis, including behavioral changes, hallucinations, delusions, cerebrospinal fluid with pleocytosis and a pathological electroencephalography with delta waves. Extensive blood tests, cerebrospinal fluid analyses and neuroimaging detected no obvious cause. No autoantibodies known to be associated with autoimmune encephalitis were found. A diagnosis of probable antibody-negative autoimmune encephalitis was made, and the patient responded well to immunotherapy. Previously, at two years of age, the patient had curative surgery for a pilocytic astrocytoma in the posterior fossa, and had severe sequels consisting of focal epilepsy, ataxia, dysarthria, secondary hypothyroidism, and the need for a ventriculoperitoneal shunt for hydrocephalus. We found no existing literature linking previous low-grade tumors in the central nervous system and/or previous neurosurgery to long-term increased risk of autoimmune encephalitis, but this case encourages further research into a possible association. Further, this case underlines the value of a newly suggested diagnostic approach to pediatric autoimmune encephalitis.

ABBREVIATIONS

AE: Autoimmune Encephalitis; BBB: Blood-Brain Barrier; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; CT: Computed Tomography; EEG: Electroencephalography; IVIG: Intravenous Immunoglobulin G; MRI: Magnetic Resonance Imaging; PCR: Polymerase Chain Reaction; PET: Positron Emission Tomography; WHO: World Health Organization

(Please Note That The Manuscript Also Mentions Several Antibodies Associated With Autoimmune Encephalitis By Commonly Used Abbreviations For Brevity And Ease Of Reading. Full-Length Names Can Be Added If Deemed Relevant By The Editor.)

INTRODUCTION

Encephalitis is the diffuse inflammation of brain parenchyma, with a wide range of clinical presentations and neurological dysfunctions. Encephalitis may be caused by infections or may occur as autoimmune or paraneoplastic conditions. The diagnostic approach involves blood tests and cerebrospinal fluid (csf) analyses to determine the cause, electroencephalography (eeg) and neuroimaging to determine the extent of the inflammation and/or demyelination and rule out important differential diagnoses. Autoimmune encephalitis (AE) is rare, with an incidence among children and adolescents of less than 2/100.000 person-years [1]. AE is associated with antibodies targeting neurons and their synapses [1]. A systematic diagnostic approach to pediatric AE has been proposed very recently by the international autoimmune encephalitis working group, including criteria for probable autoantibody-negative AE (all five criteria must be met) [2].

1) Evidence of acute or subacute symptom onset.

2) At least two of the following clinical criteria:

- Altered Mental Status/Level Of Consciousness Or EEG With Slowing Or Epileptiform Activity (Focal Or Generalized)

-Focal Neurologic Deficits

-Cognitive Difficulties

- Acute Developmental Regression

- Movement Disorder (Except Tics)

- Psychiatric Symptoms

- Seizures Not Explained By A Previously Known Seizure Disorder Or Other Condition

3) At least one the following paraclinical criteria:

- CSF inflammatory changes (leukocytosis >5 cells/mm3 and/or oligoclonal banding)

- MRI features of encephalitis

- Brain biopsy showing inflammatory infiltrates and excluding other disorders

4) No well-characterized autoantibodies associated with ae present in serum and/or csf.

5) Reasonable exclusion of alternative causes

Pilocytic astrocytoma is the most common primary brain tumor in children and adolescents, but still a rare condition, with an incidence of less than 1/100.000 person-years in children < 15 years of age[3]. In many cases, complete and curative resection is possible, and pilocytic astrocytomas rarely transform to more invasive states. Although survival rates are good, with reported relative 5-year survival rates of 95%, patients may experience sequels attributable to the tumor itself and the required treatment [3]. Autoimmune encephalitis may be a paraneoplastic phenomenon in patients with concurrent neoplasia, including cns neoplasms. An inverse correlation may also exist, as case-studies have described cns neoplasms developing after encephalitis. However, a pubmed search showed no existing literature on long-term increased risk of ae after curative treatment of cns neoplasia.

CASE PRESENTATION

At two years of age, the patient was diagnosed with a who grade 1 pilocytic astrocytoma in the posterior fossa. Initially, she was treated with a ventriculoperitoneal shunt to alleviate hydrocephalus. At ages three and four, she underwent surgical excision, and subsequent imaging showed no signs of remaining tumor mass. She had severe sequels consisting of epilepsy, ataxia, dysarthria and secondary hypothyroidism. The epilepsy was treated with levetiracetam and oxcarbazepine, and the patient reported no seizures for at least five years prior to the events reported in this case. The hypothyroidism was treated with levothyroxine. She had no complications to the ventriculoperitoneal shunt.

At age fifteen, the patient presented with acute onset of severe balance problems, myoclonic jerks in the extremities, facial dyskinesia, behavioral changes, agitation and psychotic symptoms of auditive hallucinations and delusions of religious character. Initial blood tests showed no signs of systemic infection, inflammation or metabolic disturbance. An initial csf analysis showed elevated protein of 0,94 g/l (reference interval: 0,15-0,5 g/l) and elevated immunoglobulin g of 71 mg/l (reference interval: 14-52 mg/l), no oligoclonal bands and normal levels of white blood cells, glucose and lactate. A new csf analysis four days later showed pleocytosis of 62 $\times 10^6$/l (reference interval: <5$\times 10^6$/l), elevated lymphocytes of 18$\times 10^6$/l and neutrophils of 23$\times 10^6$/l.

Microbiological analyses of CSF and blood including pcr for the most common infectious causes of encephalitis showed no viral or bacterial cause. Cytological examinations of the CSF showed reactive monocytes and no tumor-cells. Extensive CSV analyses for antibodies associated with ae (including nmdar1, ampar1+2, caspr2, lgi1 and gaba-b receptor 1) were negative. Line immunoassays of CSF for paraneoplastic markers were doubtful positive without a definite pattern for anti-gad65, sox-1, yo, ri, titin, and cv2. Further testing using indirect immunofluorescence on primate cerebellum, detected no antibodies. The patient was conferred with specialists in cns tumors in children, who found no reason to suspect paraneoplastic encephalitis.

A Ct-scan and MRI with contrast of the brain showed known sequels from her previous neurosurgery, but no acute inflammation or demyelination. MRI was repeated after 12 days with no changes. Electroencephalography (EEG) showed abnormal activity of 2-4 hz in the prefrontal, frontal and pretemporal areas bilaterally and amplitude up to 120 μv (polymorph delta activity) as single potentials or in brief trains.

Based on the clinical presentation and paraclinical findings, a diagnosis of probable antibody-negative ae was made, and immunotherapy was started. The patient responded well to intravenous immunoglobulin g (ivig) 1 g/kg for 2 days succeeded by methylprednisolone 1 g/daily for 5 days. She was discharged 14 days after admission less tormented and with less myoclonic jerks. She continued with 1 mg/kg prednisolone daily, tapered off over 6 weeks. Her agitation and psychotic symptoms were treated with antipsychotic medication (olanzapine) in collaboration with child psychiatrists.

Additional examinations included a full-body pet-ct-scan and an ultrasound of the abdomen, including the ovaries, both normal. Lumbar punctures done over the course of several months, continued to show elevated protein up to 1,53 g/l (reference interval: 0,15-0,5 g/l), fluctuating white blood cells (with no clear association with methylprednisolone-doses), and normal glucose and lactate.

14 days after termination of oral prednisolone (three months after initial symptoms), a relapse occurred with behavioral changes, facial dyskinesias and psychotic symptoms. She received acute treatment with ivig and intravenous methylprednisolone with significant improvement. Due to early relapse, oral steroids were continued for another 5 months (including tapering off over 2 months). A monthly supplement of ivig was given for four months. One year after initial symptoms, she was no longer receiving immunomodulating treatment. At this time, she had stable balance, no myoclonic jerks and no facial dyskinesia. She still received a low dose of olanzapine, managed by a child psychiatrist.

DISCUSSION

A fifteen-year-old girl, with previous, curative neurosurgery for a low-grade CNS tumor, presented with symptoms of acute encephalitis. Clinical and paraclinical findings indicated autoimmune encephalitis. CSF autoantibodies know to be

associated with AE were negatives and other differential diagnoses were excluded with extensive testing. Based on CSF abnormalities and the clinical presentation, a diagnosis of probable antibody-negative AE was made [2]. The symptoms responded well to treatment with ivig and methylprednisolone, supporting the diagnosis.

At the time of the described events, no comprehensive diagnostic guidelines existed for pediatric AE. Had we followed existing guidelines for adults [4], the patient would not have met the suggested criteria for probable autoantibody-negative AE. Very recently, the international autoimmune encephalitis working group has suggested a diagnostic approach adapted for pediatric AE [2]. According to these criteria, the patient would be diagnosed with probable antibody-negative AE.

A specific cause of the patient's AE was never determined. Repeated CSF analyses showed persistently elevated protein, suggestive of a long-lasting deficiency of the blood-brain barrier (BBB). Acute dysfunction of the BBB may be caused by trauma, ischemia, infection, toxicity or other causes of inflammation, and may in some cases lead to lasting changes and dysfunctions [5]. But literature on the precise role of the BBB in specific neuropathological conditions is very sparse. A pubmed search revealed no relevant literature on BBB dysfunction in ae or on possible long-term BBB dysfunction following primary brain tumors or brain surgery. One animal study found possible lasting dysfunction of the BBB in brain capillaries after CNS surgery.

The patient's acute encephalopathy and signs of AE may be linked to her previous low-grade brain tumor and/or the surgical treatment thereof. A possible pathogenesis may include long-term immunological changes and/or biochemical changes in CNS tissue including a decreased blood-brain-barrier function. We found no literature on lasting immunological or biochemical changes after CNS neoplasms in children or if there is an increased risk of encephalitis in patients with low-grade CNS tumors after curative surgery. As the patient's tumor and subsequent AE are both rare conditions, and their concurrence rarer still, few cases may exist, and the condition may be overlooked.

CONCLUSION

Autoimmune encephalitis is a rare condition and a structured approach to diagnosis and treatment is important when ae is suspected but no specific cause can be identified. This case report supports the usefulness of newly suggested diagnostic criteria by the international autoimmune encephalitis working group. The case also suggests the need for research into the long-term neurobiological and immunological effects of low-grade CNS tumors in children.

Consent

Written informed consent was obtained from the patient's parent.

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