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Anti-NMDA-receptor encephalitis in a 3 year old patient with chromosome 6p21.32 microdeletion including the HLA cluster

Helene Verhelst[a,*], **Patrick Verloo**[b], **Karlien Dhondt**[b], **Boel De Paepe**[b], **Björn Menten**[c], **Josep Dalmau**[d], and **Rudy Van Coster**[b]

[a] Department of Paediatric Neurology, Ghent University Hospital, De Pintelaan 185, B-9000 Gent, Belgium

[b] Department of Paediatric Neurology, Ghent University Hospital, Ghent, Belgium

[c] Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

[d] Department of Neurology, University of Pennsylvania, Philadelphia, USA

Abstract

Anti-NMDA-receptor encephalitis was initially described as a paraneoplastic disorder in young women with ovarian teratoma. We report on a 3-year-old boy who developed anti-NMDA-receptor encephalitis one month after a respiratory infection. Moreover, array-comparative genomic hybridization in this patient revealed an inherited microdeletion in chromosomeband 6p21.32, including the HLA-DPB1 and HLA-DPB2 genes. The clinical relevance of this microdeletion is discussed.

Keywords

NMDAR encephalitis; Childhood; Post-infectious; Microdeletion; HLA cluster

1. Introduction

The N-methyl-D-aspartate receptor (NMDAR) is a ligand-gated cation channel consisting of NR1 and NR2 subunits. The NR1 subunits bind glycine and the NR2 subunits glutamate, both excitatory neurotransmitters. Overactivation of NMDAR is a proposed underlying mechanism for epilepsy, dementia and stroke, whereas low activity can produce symptoms of schizophrenia.[1]

Anti-NMDAR encephalitis is a recently described disorder initially detected in young women with ovarian teratoma who developed changes of mood, behavior and personality resembling acute psychosis. The clinical picture usually progresses and seizures, decreased levels of consciousness, dyskinesias, autonomic instability and hypoventilation are seen. Good response to immunotherapy after removal of the teratoma suggested a paraneoplastic immune-mediated pathogenesis. Several studies pinpoint the NMDAR as the target of the antibody response.[2] Larger series of patients showed that the disorder also occurs in patients without teratoma, and that men and children can be affected too.[1]

We report on a 3-year-old male patient with anti-NMDAR encephalitis in whom an inherited microdeletion on chromosome 6, including the HLA cluster, was detected.

[*]Corresponding author. Tel.: +32 9332 3591; fax: +32 9332 3875. helene.verhelst@ugent.be (H. Verhelst).

2. Case study

Propositus was a previously healthy 3-year-old youngster who presented one month after a respiratory infection, with lateralized convulsions, orofacial dyskinesia and periods of agitation characterized by choreoathetotic movements alternating with periods of sleepiness during which there was almost no reaction to stimuli. Over a period of ten days he developed high grade fever. In blood signs of inflammation were detected with leucocytosis (maximal value at day 10: 18 680 WBC/μl (normal 6000–15 000)) and elevated CRP (maximal value at day 12: CRP 24.5 mg/dl (normal 0–0.5)). In cerebrospinal fluid a mild pleocytosis was seen (day 7: WBC: 33/μl, 68% lymphocytes (normal 0–8), RBC: 2/μl (normal 0)), lactate was slightly increased (23.7 mg/dl (normal 10–22)) and protein and glucose concentrations were normal. An infectious agent could not be detected. Serology for mycoplasma pneumoniae, herpes simplex virus, varicella zoster virus, cytomegalic virus, epstein bar virus, adenovirus, enteroviruses, coxsackie virus B1, B2, B3, B4, B5, influenza A, B, para-influenza 1, 2, 3, parvovirus B19, west-nile virus, borrelia, hepatitis A, B, C, human immunodeficiency virus, treponema pallidum, tuberculosis and tick borne encephalitis was negative as was the anti-streptolysin O titer. For poliovirus, measles, rubella and mumps he had serologic immunity post vaccination. Cerebrospinal fluid analysis showed negative PCR for mycoplasma pneumoniae, herpes simplex virus, varicella zoster virus, human papilloma virus and enteroviruses and showed absent antibody response for borrelia, adenovirus, enteroviruses and poliovirus. Repeated bacterial cultures of blood and cerebrospinal fluid remained negative. Also virus isolation and mycobacterial culture of cerebrospinal fluid remained negative. Acid-fast bacilli microscopy was negative on cerebrospinal fluid and gastric aspiration (three times). EEG showed a focus of rhythmic slow-waves in the left hemisphere. Initial cerebral MRI (day 6) revealed no abnormalities but repeat cerebral MRI one week later showed mild loss of cerebral and cerebellar volume, and, in addition, one small cerebellar cortical lesion hyperintens on T2-weighted and fluid attenuated inversion recovery (FLAIR) images. MRI of the spinal cord was normal.

Propositus was treated with acyclovir, ciprofloxacine, ampicilline and cefotaxime and became fever free. As signs of inflammation were detected and no infectious etiology could be found, an autoimmune mechanism was suspected but was not proven at that moment. Arguments supporting the auto-immune hypothesis were the cerebellar cortical lesion seen on MRI at day 13 and exacerbation of symptoms during intercurrent infections. Two months after presentation, after exclusion of infectious pathogens, propositus was treated with pulse doses of methylprednisolone as therapeutical trial even well without obvious effect.

During the six months after presentation he made little or no neurological progression. He had severe axial hypotonia and had no head control. His circadian rhythm was severely disturbed. He slept for long periods (up to three days) alternating with wakeful periods during which he had persistent orofacial dyskinesia and choreoathetotic movements. Only minimal social contact was possible. Oral dyskinesia and choreoathetotic movements were more severe during intercurrent infections. Initially good seizure control was obtained with valproate and levetiracetam as antiepileptic treatment. After months, seizures recurred and carbamazepine was added. He was fed by gastric tube.

Sequential cerebral MRI revealed mild progression of cerebral volume loss, supratentorial as well as infratentorial. Discrete signs of gliosis were seen in the cerebral cortex, periventricular white matter and bilaterally in the corpus striatum. As he made no progression and MRI showed signs of progressive atrophy, a neurometabolic work-up was performed. No underlying metabolic defect could be found.

Eight months after presentation the autoimmune hypothesis was revised and clinically, an anti-NMDAR encephalitis was suspected. Cerebrospinal fluid dated from two months after presentation and before steroid therapy was sent for detection of NMDA receptor antibodies.

These studies confirmed the presence of cerebrospinal fluid antibodies against NR1 subunit of the NMDA receptor (cerebrospinal fluid titer 1:40 using HEK293 cells recombinantly expressing NR1).

Meanwhile, propositus started to make some improvement starting six months after the first signs of encephalopathy. The parents regained contact with their son. He made short eye contact, started to have eye pursuit, and tried to vocalize. Because of the spontaneous positive evolution at that moment, more aggressive immunomodulating therapy was not given anymore. Intensive multidisciplinary rehabilitation was started. One year after onset of symptoms he could sit again without support, started to walk with little support, made sounds and few words. He interacted well with his environment and could understand and perform easy tasks. He also started to eat with a spoon and to drink with a straw.

Molecular karyotyping with the Agilent Human Genome CGH Microarray Kit 44 K (Agilent Technologies, Santa Clara, CA) revealed a maternally inherited microdeletion at chromosomeband 6p21.32. The deletion is ~50 kb in size, and includes the HLA-DPB1 and HLA-DPB2 genes. This deletion was confirmed with a second independent experiment. The molecular karyotype can be written as: arr 6p21.32p21.32 (33143801–33160124) × 1 (hg18).

3. Discussion

In the last few years the clinical spectrum of anti-NMDAR encephalitis has been extending from young adult women to men and children. In most aspects the clinical picture in pediatric patients with anti-NMDAR encephalitis is similar to that in adults although there are differences. The younger the patient the less likely a tumor can be identified. In a series of 32 children and adolescents only 25% had a tumor, all ovarian teratoma.[3] As in adults, most children presented with behavior and personality changes. In adolescents these behavior changes were most frequently diagnosed as psychosis. In younger children parents described temper tantrums, agitation, aggression and progressive speech deterioration as initial symptoms. Additional symptoms, seen in the majority of children are movement disorders characterized by orolinguofacial dyskinesia, choreoathetoid movements, dystonia, rigidity and stereotype movements, and also seizures. Half of the children had prodromal symptoms suggestive of a previous infection. Autonomic manifestations in children, although frequently seen, are less severe than in adults.[3]

Pediatric neurologists should include anti-NMDAR encephalitis in their differential diagnosis in all patients with unexplained encephalopathies, especially when behavior changes and movement disorders are the predominating symptom. At presentation, cerebral MRI is normal in about half of the patients or shows only aspecific hyperintense lesions on fluid-attenuated inversion recovery or T2-weighted images.[1] Early diagnosis is important as the symptoms are potentially reversible after starting immunomodulating therapy and can only be proven by detection of autoantibodies directed against NMDA receptor Fig. 1.

In propositus the diagnosis was retrospectively established eight months after presentation. The fact that he did not respond to pulse therapy with methylprednisolone and that sequential cerebral MRI revealed mild progression of cerebral volume loss was misleading and made us first exclude neurometabolic underlying causes. However it is known that in patients who do not recover early from their neurological dysfunction generalized atrophy predominantly fronto-temporal and more seldom scattered hyperintense lesions on fluid-

attenuated inversion recovery or T2-weighted images suggestive for gliosis can be seen.[1] But a recent long-term observational study showed that even severe protracted neurological deficits and cerebral atrophy is potentially reversible suggesting rather a functional than a structural neuronal damage underlying the pathogenesis.[4]

Underlying genetic predisposing factors for anti-NMDAR encephalitis are not known yet. The case presented here might suggest a possible link with polymorphisms in the HLA class II cluster. In epidemiological and genetic studies associations between HLA class II alleles and many autoimmune diseases were found. Many polymorphisms in HLA class II genes are known as predisposing factors for autoimmunity. However, it is still hard to tease apart the precise contributions of each individual allele to the overall risk of developing an autoimmune disease.

In the patient presented here, in addition to anti-NMDAR encephalitis a microdeletion at the short arm of chromosome 6 including the HLA-DPB1 and HLA-DPB2 genes was detected. Although deletions of this region have been reported in normal individuals, this genomic finding in our patient opens the debate whether variation in HLA genes copy numbers is a possible predisposing factor for autoimmune diseases, and, more specifically in our patient, a risk factor for developing anti-NMDAR encephalitis. The possible link between the HLA region and autoimmunity is illustrated by several reports of polymorphisms in the HLA-DPB1 gene as risk factor for development of autoimmune diseases including multiple sclerosis,[5] hyperthyroid Graves' disease,[6,7] early-onset myasthenia gravis[7] and sarcoidosis.[8] But, as far as we know, microdeletions of HLA genes have not been linked to auto-immunity. However, the known polymorphisms within the HLA locus are not restricted to the exons but extend into the promoter regions and, in this way, may regulate the expression of the HLA genes. In mouse models, it is shown that different expression of HLA genes influences macrophage activation and inflammation. Elevated or decreased number of MHC class II molecules at the immunological synapse between the antigen presenting cell en the T helper cell modulates their interaction.[9]

The microdeletion detected in propositus has also been detected in his mother. Since she did not suffer from any auto-immune disease we can not exclude that the microdeletion might be a benign variation. However, microdeletion variants could have variable penetrance. Moreover, if the microdeletion contributes to the phenotype we can only consider the micro-deletion as a predisposing factor in developing autoimmune diseases. It is knows that, in addition to possible underlying genetic variants, environmental factors are supposed to play a role in triggering an autoimmune process. Differences in exposure to environmental factors may explain the difference in phenotype between propositus and his mother.

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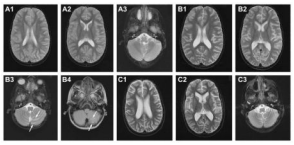

Fig. 1.

Sequential cerebral MRI (A on day 6, B on day 13, C after 8 months) showing progressive cerebral and cerebellar volume wasting. In addition one discrete cerebellar cortical lesion hyperintens on T2-weighted (B3) and fluid attenuated inversion recovery (FLAIR) images (B4).