A 64-YEAR OLD PSYCHIATRIC PATIENT SUFFERING FROM DEPRESSION, VERTIGO AND SUICIDE THOUGHTS WITH NYSTAGMUS AND DIPLOPIA

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A 64 year old patient was referred to the psychiatric ward due to a depressive mood and suicide thoughts. An antidepressant treatment was started. Intermittently, he showed a rightward horizontal gaze-evoked nystagmus. We arranged a cerebral magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis, which revealed an autoimmune disorder - dipeptidyl-peptidase-like protein 6 (DPPX) antibody - which was the probable underlying cause. The patient was treated with steroids and azathioprine which improved his condition substantially. The case emphasizes the relevance of putative autoimmune etiology of acute psychiatric diseases.

Key words: Psychosis, nystagmus, autoimmune encephalitis, dipeptidyl-peptidase-like protein 6 antibody, immune suppression

Introduction

Antibody-associated neuropsychiatric syndromes were first identified in the 1980ies and initially allocated to different forms of cancer as paraneoplastic syndromes (1, 2, 3, 4). Meanwhile a plenty of antibodies directed to neuronal structures have been detected, which have not necessarily to be related to tumors (5, 6, 7, 8). In 2007 the anti-NMDA [N-methyl-D-aspartate]-receptor encephalitis was discovered, which is related to ovarian carcinoma in some 50 %. Apart from schizophreniform symptoms, the patients of this quite frequent disorder – more than 1000 documented cases - may suffer from dyskinesia, dystonia or epileptic seizures. Likewise, potassium channel antibody associated diseases play an important role (voltage gated potassium channel complex, VGKC), which bind to proteins such as LGI1 [leucine-rich, glioma inactivated 1] or Caspr2 [contactin associated protein] (6). LGI1-encephalitis often show psychosis-like findings including epilepsy in older men, whereas Caspr2 is often related to the so-called Morvan syndrome, which is characterized by neuromyotonia and insomnia or confusion. Some practically important differential diagnoses of autoimmune encephalopathies with their core syndromes are summarized in table 1.

DPPX [dipeptidyl-peptidase-like protein 6] - associated encephalopathies are comparably rare and in most cases not associated with tumors. This IgG subclass antibody regulates the Kv4.2 [potassium channel, voltage dependent] channel, which is abundant in brain and myenteric plexus. Often paranoid symptoms or mutism are observed in addition to weight loss and diarrhea (5). The channel is possibly involved in soma-dendritic signal and decreases neural back propagation (9). The latter may have importance in neural plasticity or long-term poten-}

Case report

A 64-year-old patient was referred to the psychiatric ward due to suicide thoughts, depression


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and increasing rotary vertigo for a few weeks by his General Practitioner. He had a history of alcohol and nicotine abuse but was completely abstinent for at least 4 years. A chronic pancreatitis hyperuricemia were preexisting. An obsessive-compulsive disorder - thoughts - was diagnosed in the run-up of the admission. He had no autonomic complaints and slept well. He worked as truck driver and was divorced 15 years ago having neither contact to his daughter nor to his earlier friends. 

On admission, his psychopathology showed a cooperative man, well orientated with only minimal brain impairment without psychotic symptoms. The leading symptoms were recurrent suicide impulses. Auscultation revealed a 2/6 systolic murmur (Punctum maximum at Erb). Neurological findings including reflex status of the upper and lower limb were initially normal apart from a slight ataxia. Routine CCT revealed a minimal bifrontal and cerebellar atrophy and an old white matter lesion in the left lobus parietalis inferior. The MRI of the brain confirmed the lacunar stroke and an II° microangiopathic leuencephalopathy. On a regular base the patient took aspirin (100mg sid), simvastatin (20 mg hs), pantoprazol (40 mg hs), mirtazapine (45 mg hs).

During a word round the patient’s eye movements were conspicuous. He complained of an increasing vertigo and showed a horizontal gaze-evoked nystagmus with a vertical component, pronounced when looking to the right side. Additionally, the ataxia was somewhat more emphasized. He did not complain of nausea. Ear nose throat specialist examination did not reveal a peripheral disorder. The ophthalmologist described an incomplete paresis of the right oculomotorius nerve. The diagnosis was extended to reveal the origin of the encephalopathy (Time of Flight MRI (TOF), echocardiography, long-term ECG, neurosonography, abdominal sonography, CSF). The TOF revealed a microaneurysm of the anterior communicans, neurosonography a slight atherosclerosis, echocardiography showed a minimal left cardiac hypertrophy, and abdominal sonography a hepatopathy in connection with a chronic pancreatic atrophy.

The cerebral MRI did not show inflammatory changes of acute ischemia but only a slight degree 2 subcortical glioses with global cerebral atrophy. The EEG only showed a normal basic rhythm with a few interictal single sharp waves. The ABEP [auditory brainstem evoked potentials] indicated a brain stem lesion, which could not be localized. VEP (visual evoked potentials) could not be interpreted due to the nystagmus. The CSF revealed positive oligoclonal bands as a hint for an immunological process, otherwise no critical pathological results (clear, 1 cells/µl, no erythrocytes, protein, albumine, glucose and lactate within normal range) were found. Finally we could confirm Anti-DPPX-antibodies (di-peptidyl-peptidase-like protein 6 – subunit protein of the potassium channel) which could explain the exacerbated encephalopathy including psychiatric symptoms.

Having a normal TMTP [thiopurine-methyltransferase] activity treatment with azathioprine was initiated (50 sid or bid according to WBC) and prednisolone (50 mg per day, including a reduction scheme) was started. Within 4 to 5 weeks time the patient improved with normal cognitive test results (DemTect, Mini-Mental-Status-Test). He could be discharged in sufficient state of health and was referred to the out-patient clinic. He was again seen a month after discharge from the ward showing again a deterioration, which well responded to an intravenous pulse therapy with prednisolone (500 mg per day) and an increased dose of azathioprine (150 mg per day). CSF analysis was repeated and oligoclonal bands were no longer present. Since the discharge from the ward, no relapses occurred for 9 months and no further admission to the hospital was necessary. The author thanks the patient for his written informed consent to publish the case.

**Discussion**

We saw a 64-old patient with psychiatric symptoms who developed a nystagmus during his treatment on the psychiatric ward. The neuro-somatic diagnostics revealed an autoimmune disease which could be treated with success and which improved his well being in addition to his symptomatic psychiatric medication. The case report emphasizes the relevance of differential diagnoses of autoimmune psychiatric disorders in patients with acute psychotic symptoms.

The DPPX antibody syndrome is a rare disorder which - like a chameleon - can vary in its clinical presentation. Therefore, it is an advantage to consider both neurological and psychiatric disorders in a broader sense, especially autoimmune diseases (Table 1). The combination of affective disorder and a neurological deficit gave the initial hint to look for an organic source of the disease. The major benefit for patient was the specific immune suppressive treatment option which improved both symptoms and life quality. Moreover, oncological treatment may help in paraneoplastic disease if available. Psychiatric treatment is guided by the syndrome of psychopathology. No standard causal treatment exists and, as a rule, the therapy has off-label character. In general, steroids, intravenous immune globulins, azathioprine or cyclophosphamid are mentioned in the literature (6, 7, 8). For sure, controlled studies will be necessary to improve the safety and efficacy of strategies and approaches.
**Table 1:** Summary of selected autoimmune encephalitic processes associated with psychopathological symptoms

<table>
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<tr>
<th>Antibody directed to</th>
<th>Core symptoms and findings</th>
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| NMDA-receptor        | Psychosis, perioral dyskinesia, epileptic fits, dystonia, coma - frequently in children  
3/4 women, often associated with ovarial tumors |
| LGI1                 | Dystonia of face and arm, fits, amnesia, psychosis, hyponatriemia, |
| Caspr2               | Neurromyotonia, Morvan Syndrome*) |
| AMPA receptor        | Epileptic fits, Amnesia, psychosis |
| DPPX                 | Limbic encephalitis, mutism, paranoia |
| GABA<sub>B</sub> receptor | Epileptic fits, amnesia |
| nGluR5               | Personality change, affective instability, Orphelia syndrome**), associated with Hodgkin lymphoma |
| Glycine receptor     | Cognitive impairment, hyperexcitability, PERM, stiff person syndrome |
| Hu, Ma1, Ma2, CV-2, ANNA3 | Limbic encephalitis (paraneoplastic): fits, mnestic deficit, confusion, psychosis, depression |
| Hu (70%) and         | PERM syndrome (paraneoplastic), variable: limbic, brain stem, cerebellar, motor, sensory, myenteric symptoms |

*) limbic encephalitis with neurromyotonia  
**) Hodgkin associated with autoimmune limbic encephalitis due to mGluR5.

**Abbreviations:**  
NMDA: N-Methyl-D-Aspartate  
Caspr: contactin associated protein  
AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid  
LGI1: Leucine-rich, glioma inactived 1  
mGluR5: metatropic glutamate receptor 5  
GABA: gamma amino butyric acid  
PERM: progressive encephalomyelitis with rigidity and myoclonus  
Hu, Ma: initials of the first patient  
ANNA: antineuronal antibody  
CV-2 (CRPM5): anticollapsin response-mediator protein

**References**

PSIHJIATRIJSKI PACIJENT STAR 64 GODINE KOJI PATI OD DEPRESIJE, VERTIGA I SUICIDALNIH IDEJA SA NISTAGMUSOM I DIPLOPIJOM

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Ključne reči: psihoza, nistagmus, autoimuni encefalitis, dipeptidyl-peptidase-like protein 6 antibody, imuna supresija