CASE REPORT

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Acute psychosis followed by fever – Malignant neuroleptic syndrome or viral encephalitis?

Akutna psihoza praćena febrilnošću – Maligni neuroleptički sindrom ili virusni encefalitis?

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Abstract

Introduction. Neuroleptic malignant syndrome is rare, but potentially fatal idiosyncratic reaction to antipsychotic medications. It is sometimes difficult to diagnose some clinical cases as neuroleptic malignant syndrome and differentiate it from the acute viral encephalitis. **Case report.** We reported a patient diagnosed with acute psychotic reaction which appeared for the first time. The treatment started with typical antipsychotic, which led to febrility. The clinical presentation of the patient was characterised by the signs and symptoms that might have indicated the neuroleptic malignant syndrome as well as central nervous system viral disease. In order to make a detailed diagnosis additional procedures were performed: electroencephalogram, magnetic resonance imaging of the head, lumbar puncture and a serological test of the cerebrospinal fluid. Considering that after the tests viral encephalitis was ruled out and the diagnosis of neuroleptic malignant syndrome made, antipsychotic therapy was immediately stopped. The patient was initially treated with symptomatic therapy and after that with atypical antipsychotic and electroconvulsive therapy, which led to complete recovery. **Conclusion.** We present the difficulties of early diagnosis at the first episode of acute psychotic disorder associated with acute febrile condition. Concerning the differential diagnosis it is necessary to consider both neuroleptic malignant syndrome and viral encephalitis, i.e. it is necessary to make the neuroradiological diagnosis and conduct cerebrospinal fluid analysis and blood test. In neuroleptic malignant syndrome treatment a combined use of electroconvulsive therapy and low doses of atypical antipsychotic are confirmed to be successful.

Key words:
neuroleptic malignant syndrome; encephalitis, viral; diagnosis; diagnosis, differential; treatment outcome.

Apstrakt

Uvod. Maligni neuroleptički sindrom je retka, potencijalno fatalna, idiosinkratska reakcija na antispihotičnu terapiju. U nekim kliničkim slučajevima je teško postaviti diferencijalnu dijagnozu između malignog neuroleptičnog sindroma i akutnog virusnog encefalitisa. **Prikaz bolesnika.** U ovom radu prikazan je bolesnik kod koga je prvi put dijagnostikovana akutna psihotična reakcija i započeto lečenje tipičnim antipsihotikom, nakon čega je došlo do razvoja febrilnosti. Klinička slika odlikovala se znakovima i simptomima koji su mogli ukazivati i na maligni neuroleptični sindrom i na virusno oboljenje centralnog nervnog sistema. U cilju detaljnog dijagnostikovanja urađene su dodatne procedure: elektroencefalografija, magnetna rezonanca glave, lumbalna punkcija i serološke analize likvora. S obzirom na to da je nakon toga isključen virusni encefalitis i postavljena dijagnoza malignog neuroleptičkog sindroma, bolesniku je odmah isključena antipsihotična terapija. Lečen je prvo simptomatskom terapijom, a potom atipičnim antipsihotikom i elektrokonvulzivnom terapijom, nakon čega je došlo do potpunog oporavka. **Zaključak**. Prikazane su teškoće rane dijagnoze kod prve epizode akutnog psihotičnog poremećaja udruženog sa akutno nastalim febrilnim stanjem. Diferencijalnodijagnostički je neophodno razmotriti pojavu malignog neuroleptičkog sindroma i virusnog encefalitisa, odnosno potrebno je uraditi neuroradiološku dijagnostiku, i analizu likvora i krvi. U terapiji malignog neuroleptičkog sindroma potvrđena je uspešnost kombinovane primene elektrokonvulzivne terapije i niskih doza atipičnog antipsihotika.

Ključne reči:
neuroleptički maligni sindrom; encefalitis, virusni; dijagnoza; dijagnoza, diferencijalna; lečenje, ishod.

Introduction

In the psychiatric clinical practice, it is sometimes very difficult to differentiate an organic acute psychotic reaction from neuroleptic malignant syndrome (NMS) [1, 2]. NMS may mask an infectious disease of the central nervous system (CNS), while, on the other hand, CNS infection itself may be a risk factor of faster and easier onset of NMS as a response

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to the applied antipsychotic drug therapy [3, 4]. However, acute viral encephalitis, whose clinical picture primarily includes pronounced psychiatric phenomenology, constitutes a particular problem.

Acute viral encephalitis is a non-purulent inflamatory disease of the brain, most commonly caused by *Herpes simplex* viruses – type 1 (HSV-1) and type 2 (HSV-2), enteroviruses, or arboviruses [4]. The onset is abrupt, acute and followed by high temperature and headache. Disorders of consciousness, personality and mood (particularly in cases of HSV encephalitis), epileptic seizures, hemiparesis, or meningeal signs and symptoms are also common occurances. The most accurate diagnostic tool is brain biopsy, but it is non-applicable. The other reliable parameter is the polymerase chain reaction (PCR) test, with the sensitivity of 95%, and specificity of 100% for *Herpes simplex* viruses. However, the other laboratory values are not considered to be a reliable aid in the diagnosis of viral encephalitis, since the serological test of the cerebrospinal fluid (CSF) very often remains within the normal range.

NMS is a rare (0.02–3.22%), idiosyncratic adverse reaction to antipsychotic drug therapy, and it is not directly associated with antipsychotic drugs dosage [1, 5]. Such idiosyncratic adverse reaction to antipsychotic drug therapy occurs as a result of the polymorphism of dopamine receptors and it is associated with individual genetic vulnerability to antipsychotic medications. All antipsychotics, both typical and atypical, might cause NMS, but high-potency antipsychotic medications (haloperidol, fluphenazine) are considered a more common cause of this syndrome [6]. The etiology of NMS has not been fully elucidated yet; it is thought that blockade of the dopamine transmission in the nigrostriatum causes muscle rigidity, tremor and rhabdomyolysis, while the dopamine blockade in the hypothalamus leads to the changes in thermoregulation and hyperthermia [2]. Death occurs as a result of respiratory depression, cardiovascular collapse, renal dysfunction, rhabdomyolysis, disseminated intravascular coagulation (DIC) or pulmonary embolism. In recent years reduction in mortality caused by NMS has been registered, i.e. until 1970 mortality rate was up to 76%, but since 1980 it has been gradually reducing and now it is 10–20% [7]. Some 90% of patiens the developed NMS recover within 2 to 14 days. This period was prolonged up to 35 days in patients receiving a depot preparation of antipsychotic drug [7].

In all the patients who had high temperature accompanied by the change in mental status, the lumbar puncture was indicated in order to exclude a possible CNS infection. Lumbar puncture and the electroencephalogram (EEG) are essential diagnostic procedures for elucidating and determining the etiology of the altered mental status [8, 9]. EEG is an early and sensitive indicator, so it can be used to help in the differential diagnosis of some cases. During the acute phase of the disease focal abnormalities are often recorded on EEG. The severity of EEG abnormalities does not usually correlate with the severity of the disease (encephalitis), but their improvement predicts good prognosis [10, 11].

Case report

A 22-year-old soldier prior to joining the Army functioned adequatelly in all the spheres of his life. The patient was treated in the regional military hospital, diagnosed with acute psychotic reaction. As soon as his general condition deteriorated (after 13 days), he was referred to the Clinic for the Internal and Emergency Medicine of the Military Medical Academy (MMA), where he was kept for 3 days, and then transferred to the MMA's Psychiatry Clinic for further treatment which lasted 39 days. So, his treatment lasted two months altogether.

Based on the heteroanamnestic data (the mother) and the available medical documentation, it was found out that 10 days prior to his admission to the regional military hospital his mood altered: he was nervous, tense, inclined to conflict situations, physically agressive, complaining of severe headaches and caugh. On admission he was psychomotorically agitated, with paranoid and bizarre sexual delusions. The patient was initially treated with high doses of anxiolytics – diazepam 50 mg/day and on the 11th day since the start of the treatment he was prescribed haloperidol, parenterally, at a total daily dose of 30 mg. As a reaction to this therapy a sudden change in his mood occured (he became negativistic and mutistic). A day after the antypsychotic therapy was administered, his body temperature elevated up to 38°C, and some laboratory values increased: creatine phosphokinase (CPK) – 1706 U/L (normal values 26–200 U/L), leucocytes – 15,000 $\times 10^9$/L (normal 4,000–10,000 $\times 10^9$/L), ALT – 135 U/L (normal 10–49), AST – 73 U/L (normal 0–37 U/L). As for the neurological status rigidity and tremor were registered in all the extremities. As the differential diagnosis NMS and viral encephalitis were considered. Antipsychotic therapy was immediately stopped. Because of the suspected encephalitis (headache, cough, febrility, altered state of consciousness), computed tomography (CT) of the head and lumbar puncture were performed. CT was normal. The lumbar puncture showed 8 lymphocytes/mm^3 (normal values – lymphocytes $\leq$ 5 mm^3). The serological tests of the CSF were normal.

Due to the poor somatic state the patient was transferred (on the day 13) to the Clinic for Internal and Emergency Medicine of the Military Medical Academy. On admission he was conscious, disoriented, poorly communicative, hypertensive (200/120 mmHg), febrile (38.6ºC), with rigidity and tremor reported in his neurological status. The antibiotic (ceftriaxone 2 g/day), antihypertensive and anticholinergic (biperiden 10 mg/day) therapies were immediately started. After the second lumbar puncture analysis of the cerebrospinal fluid showed 5 elements/mm^3 (normal – lymphocytes $\leq$ 5 mm^3), glucose 5.7 mmol/L (normal values 2.2–4.4 mmol/L); other findings from cerebrospinal fluid (CSF) (serological analysis, proteins) were normal. On the day 14 after the initiation of the treatment EEG reading indicated theta dysfunction in the right frontocentral region.

Since the differential diagnosis ruled out viral encephalitis, on the day 15 from the start of the tretament the patient was transferred to the Psychiatry Clinic. Upon the admission

to the Clinic he was febrile (38.6ºC) and very agitated. The blood values obtained by the repeated laboratory tests showed the leucocyte count of 20,000 × 10^9/L, and the erythrocyte sedimentation rate (SE) of 30 mm/1h (normal values < 25 mm/1 h). His blood pressure was elevated (160/110 mmHg). The rigidity in muscles accompanied by the pronounced tremor and excessive sweating was still present in his neurological status. The slowness of movement and speech, disorientation in time and space and confusion were identified by psychiatric observation. In the course of his treatment daily oscillations from somnolency to the state of agitation with paranoid delusions were registered. At that point the patient was treated only with symptomatic therapy (intravenous rehydration polyvitamin, diazepam in high doses – 50 mg/day, antibiotics – ceftriaxone 2 g/day, antihypertensives).

On the day 22 after the start of the treatment the patient's laboratory values and blood pressure were normalized, so his antihypertensive and antibiotics therapy was withdrawn. The rigidity and tremor also disappeared and during the examination of the muscle tone an active muscle resistance was noted. With the improvement of his somatic condition the clinical picture of confusion, delirium syndrome was becoming more pronounced. Therefore, an atypical antypsychotic drug (clozapine 75 mg/day) and an affective stabilizer (valproate 1500 mg/day) were introduced into his therapy on the day 23 from the start of the treatment. Since the above-described clinical picture persisted even after the administered antipsychotic drug therapy, electroconvulsive therapy (ECT) was added to his therapy on the day 28, with the informed consent of the patient's close relative. The course of ECT consisted of 4 applications administered in the 2 following weeks.

EEG was performed 3 times (on the days 14, 21 and 34) and each time theta dysfunction was recorded in the right frontal region. The patient also underwent magnetic resonance imaging (MRI) of the head with contrast – the findings were normal. One month after the beginning of the treatment the patient was clinically stable, with no symptoms of confusion, delirium syndrome, but with persistent paranoid delusions. The therapy was not changed and on the day 48 the fourth EEG was performed, which, in comparison to the previous findings, displayed the phase of recovery. The fifth EEG, carried out at the completion of his hospital treatment (on the day 75), was normal. Medical check-ups in an outpatient setting (the first after 2 weeks and later repeatedly at one-month intervals), showed that the patient was in stable remission, with complete distancing from paranoid delusions. He underwent antipsychotic drug therapy with clozapine and an affective mood stabilizer (valproate) given at the remission-maintaining doses of 50 mg and 1000 mg *per* day respectively. Six months upon the completion of his hospital treatment full recovery with normal clinical psychiatric and neurological findings was recorded. The laboratory values of biochemical and hematological values fell within the normal ranges. The EEG readings were normal. As the patient's medical condition and recovery remained stable, the therapy was withdrawn.

Discussion

NMS most often occurs during the first administration of antipsychotic drug therapy, or after the increase in the dose of antipsychotic. Risk factors associated with the development of neuroleptic malignant syndrome range from the ambient temperature rise, dehidration, agitation or catatonia, the use of high-potency neuroleptic drugs or depot preparations, to an organic brain damage and the concomitant use of lithium or anticholingerics.

To diagnose NMS it is necessary to take a thorough medical history, perform somatic and neurological examination and monitor laboratory parameters [12]. For now, there are no generally accepted diagnostic criteria for NMS, but the most commonly used criteria are DSM IV [13] and Levenson criteria which require the existence of all the 3 major symptoms (fever (> 38ºC), rigidity, increased CPK), or 2 major and 4 out of 7 minor symptoms (tachycardia, abnormal blood pressure, tachypnea, leukocytosis (10,000–40,000 × 10^9/L), altered consciousness, sweating) [7, 14].

The presented patient developed a clinical picture of NMS within 24 h after the administration of the typical antipsychotic, haloperidol, in the daily dose of 30 mg. Information about the occurence of a strong headache and cough in early stages of the disease required a detailed examination of the patient, because the differential diagnose raised the question whether NMS masked the primary CNS infectious disease [3, 4, 14]. For this reason and also because of the lymphocytic pleocytosis (8 limphocytes/mm^3 – on the day 10 from the start of the treatment), the patient was thoroughly neurologically and infectologically examined (lumbar puncture, serological analysis CSF, CT, MRI, EEG).

EEG was performed on several occasions (on the days 14, 21, 34, 48 and 75). Theta dysfunction was registered in the right frontocentral region, corresponding with the period when confusiondelirium syndrome was most prominent (on the days 14, 21 and 34). As the patient's clinical findings improved, the EEG results improved as well (on the day 48 and 75).

Such changes in EEG were also mentioned by other authors who were describing NMS [15]. Very few studies so far performed have established that it is most likely that dopamine blockade leads to changes in neural pathways, causing abnormal EEG [16].

The diagnostic criteria for encephalitis [10, 11] are: general signs of inflammation, including changes on the skin, mucous membrane and lymph nodes; neurological signs (hemiparesis, aphasia, ataxia, pyramidal signs deficits, autonomic dysfunction, etc.); changes in laboratory blood tests (lymphocytosis is characteristic of viral encephalitis, while leucopenia and thrombocytopenia are characteristic of viral hemorrhagic fevers); changes in X-ray of the lungs; changes in EEG readings, most often temporofrontally slow rhytm or recurrent complex [17]; changes in CT or MRI of the head (with contrast), such as hyperintensity, edemas, hemorrhage, or inflamation; temporal lobe hyperperfusion registered on Single Photon Emission Computed Tomography (SPECT); positive findings obtained by lumbar puncture: lymphocytic

pleocytosis (> 5 lymphocytes/mm^3), glucose normal, proteins normal/or slightly elevated. The results of > 5 lymphocytes/mm^3 are found in 95% of acute viral encephalitis cases; serological analysis of CSF.

Table 1 shows that the patient met all the criteria for NMS, while the evidence for acute viral encephalitis was a suspicious CSF finding (borderline lymphocytes *per* mm^3), as well as general signs at the biginning of the treatment (headache, cough). The changes verified in EEG are described in NMS, as well as in acute viral encephalitis [10, 15, 16].

activity in the brain. First effects of ECT therapy are usually registered after the fourth application of ECT [14], which is exactly the number of treatments the respective patient received. The application of ECT should be particularly considered when it comes to patients who do not show any signs of improvement even 48 h after the pharmacological treatment, or when the clinical picture is not clear, i.e. when the cause of the symptoms could be NMS, malignant catatonia, or mood disorder [14].

Table 1

Comparison of diagnostic criteria for neuroleptic malignant syndrome (NMS) and viral encephalitis in the presented case

Diagnostic criteria	Criteria present
Features common to both disorders	
hyperthermia	+
leukocytosis	+
altered consciousness	+
EEG: diffuse slowing and focal abnormalities	+
Distinguishing features	
Features more common to NMS	
elevated CK	+
muscle rigidity	+
tachycardia	+
tachypnea	+
abnormal blood pressure	+
diaphoresis	+
Features more common to viral encephalitis	
general signs of infection, headache, cough	+
focal neurologic signs	-
MRI: focal signs	-
abnormal chest x-ray findings	-
cerebrospinal fluid: pleocytosis	Borderline findings

EEG − electroencephalogram; CK − creatine kinase; MRI − magnetic resonance imaging.

After an episode of NMS it is necessary to include antipsychotics into the therapy again, in order to control psychiatric symptoms. The scientific literature contains evidence that rechallenging the patient with the same antipsychotic results in NMS recurring in 5 out of 6 cases. The use of lower potency antipsychotics is safe in 9 out of 10 cases. The introduction of atypical antipsychotic in a lower dose with regular monitoring for symptoms of NMS is one of the safest methods of treatment [2].

After the withdrawal of NMS symptoms (on the day 23 from the start of the treatment) the patient presented in this case was given clozapine in small doses [2, 18] and ECT was performed, as well.

Electroconvulsive therapy can reduce hyperpyrexia, perspiration, delirium, probably by modulating the dopamine

Conclusion

We presented the difficulties in early diagnosis at the first episode of acute psychotic disorder associated with acute febrile condition. For the differential diagnose it is necessary to consider potentially fatal NMS and viral encephalitis, i.e. neuroradiological diagnostics, cerebrospinal fluid analysis and laboratory tests need to be done. In the treatment of NMS, in addition to excluding the prescribed antipsychotic and administration of a symptomatic therapy, a combination of ECT and low doses of atypical antipsychotic proved to be successful. Outpatient follow-up (6 months after the hospital treatment), alongside with monitoring of laboratory parameters and follow-up EEG, showed a complete recovery of the patient.

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