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# FEVER AND ALTERED CONSCIOUSNESS ARE NOT ALWAYS EQUAL TO CENTRAL NERVOUS SYSTEM INFECTION: NEUROLEPTIC MALIGNANT SYNDROME IN A 15 - YEAR - OLD GIRL*

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**SUMMARY: Ünal F, Hızlı Ş, Özyürek H, Sonuvar B. (Departments of Child Psychiatry and Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Fever and altered consciousness are not always equal to central nervous system infection: neuroleptic malignant syndrome in a 15-year-old girl. Turk J Pediatr 1996; 38: 505-510.**

**Neuroleptic malignant syndrome, the most serious and potentially fatal side effect of neuroleptics, is characterized by altered consciousness, extrapyramidal symptoms, hyperthermia, elevated plasma creatine phosphokinase and leukocytosis. In the child and adolescent population, the syndrome may be underrecognized or underreported. We describe a 15-year-old girl who developed neuroleptic malignant syndrome after a single injection of two different neuroleptics. We find the case interesting because the patient's course was unusual, and she was treated successfully with the combination of diazepam and biperiden. Our aim is to discuss several aspects of the syndrome through this case, particularly the problem of recognition.** *Key words: neuroleptic malignant syndrome, adolescent, diazepam, biperiden, haloperidol, chlorpromazine.*

Neuroleptic drugs (antipsychotics) produce numerous side effects, including serious extrapyramidal symptoms consisting of akathisia, dystonia, tremor, akinesia, rigidity, tardive dyskinesia and neuroleptic malignant syndrome (NMS). Among these side effects, the most serious and potentially fatal complication is NMS[1]. The syndrome is characterized by altered consciousness; extrapyramidal symptoms such as muscle rigidity, dystonia, akathisia and tremor; symptoms of autonomic dysfunction such as hyperthermia, tachycardia, hypertension or hypotension; diaphoresis; elevated plasma creatine phosphokinase (CPK); and leukocytosis[2, 3].

NMS typically develops within days of a recently initiated course of neuroleptic drug treatment. Potential risk factors for NMS may include dehydration, agitation, affective disorder, intramuscular drug application and a higher drug dosage[4, 5]. In the last decade, numerous reports have provided sufficient data to estimate the frequency of NMS in patients treated with neuroleptic drugs[6-10]. Risk estimates

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for NMS on exposure to neuroleptic drugs vary between 0.07 percent and 2.44 percent. The mean estimated frequency from pooled data is reported to be 0.67 percent. In the child and adolescent population, NMS may be underdiagnosed or underreported, perhaps due to the infrequent use of neuroleptic drugs in this population as well as difficulties in recognizing the condition. In Addonizio et al.'s[12] review covering all of the 115 cases reported in the English literature, 15 patients were in the range of 10 to 19 years old. Other investigators have reported single cases or small series of children and adolescents who developed NMS[13-20].

The case we describe here is a 15-year-old girl who developed NMS after a single injection of two different neuroleptics. We find the case interesting because the patient's course was not typical, she was treated successfully with the combination of diazepam and biperiden. Our aim is to discuss several aspects of NMS through this case, particularly the problem of recognition.

## Case Report

The patient was a 15-year-old female with no history of medical or psychiatric illness. Her father was reported to have the diagnosis of schizophrenia, paranoid type. There was no history of other psychiatric illness in the family.

One week prior to her admission to our hospital she developed an acutely progressing clinical picture consisting of insomnia, agitation and paranoid delusions. This clinical picture was considered to be a psychotic episode by a local hospital, and a single intramuscular injection of the combination of haloperidol 5 mg and chlorpromazine 25 mg was administered. Approximately eight hours after this injection, a gradually progressing clinical picture consisting of fever, fluctuating consciousness, weakness and muscle rigidity developed. She was admitted to the local hospital with the preliminary diagnosis of encephalitis because of her high fever, confusion and neck stiffness. All of the laboratory findings including urine, blood. cerebrospinal fluid (CSF) analysis and EEG were reported to be normal. It was remarkable that plasma creatine phosphokinase (CPK) was not evaluated in the local hospital. Dexamethasone 4 mg g.i.d., mannitol 120 cc t.i.d. and nifedipine 15 mg t.i.d. were administered for the additional symptom of hypertension, but she was referred to the university hospital because a clinical change was not observed within five days with that treatment.

On admission to our hospital, the patient's physical, neurological and psychiatric examinations were remarkable for hyperthermia (38 °C), confusion, agitation, possible auditory and visual hallucinations, "cogwheel" muscular rigidity, labile blood pressure and diaphoresis. Abnormal laboratory findings included a WBC of 12,300/$mm^3$, and a CPK of 832 IU/L. Routine blood, urine, CSF analysis, blood and urine cultures, $B_{12}$, serum protein electrophoresis, anti-DNA, complement

$C_3/C_4$, EEG, ECG, abdominal ultrasonography and cranial computed tomography (CT) studies were normal. The patient fulfilled the criteria given by Caroff et al.[2] and Levenson[21] for the diagnosis of NMS, and diazepam 20 mg and biperiden 10 mg were administered daily. Five days later, her agitation disappeared and plasma CPK returned to normal levels. Although her confusion, hallucinations, muscular rigidity and autonomic dysfunction symptoms diminished gradually, the patient had recovered completely on the 20$^{th}$ day of that treatment. In the drug-free follow-up period of six months, she had neither psychiatric nor medical symptoms.

## Discussion

With the increasing use of psychotropic drugs in the child and adolescent population, NMS has become an important diagnostic consideration for the pediatrician. Many cases of NMS may go unrecognized, particularly in the early stages of development of the syndrome[6]. We believe that this fact is particularly relevant in children and adolescents, as it was the case in our patient. Although she had almost all of the symptoms of the syndrome, NMS remained unrecognized in the local hospital. This may be due to insufficient knowledge about NMS or a lack in the information sources. Her parents helped a great deal by explaining that the fever and the confusional state had begun immediately after the injection. We believe that assumptions of the family about the etiology of the disorder should be taken into account.

NMS patients come to pediatricians mostly with altered consciousness and fever. Medical conditions to be considered in the differential diagnosis of this clinical picture include systemic and central nervous system (CNS) infections, septicemia, CNS mass lesions, metabolic conditions and autoimmune diseases. It is noteworthy that these conditions can be associated with NMS or superimposed. NMS is sometimes confused with intoxication with strychnine or CO, serotonin syndrome, malignant hyperthermia, heat stroke and lethal (psychogenic) catatonia[2,5].

Clinical pictures of intoxication, serotonin syndrome, malignant hyperthermia, heat stroke or lethal catatonia are infrequent but often considered, because of their specific etiology, prodromal and morbid features. CNS mass lesions, metabolic conditions and autoimmune diseases are also easy to detect with cranial CT or specific laboratory tests.

CNS infections are more frequently seen and may be a perplexing problem in the differential diagnosis, thus should be discussed in detail. In meningitis cases, fever is the cardinal sign, while headache, lethargy and irritability are also seen. In CSF findings, increased WBC and protein as well as decreased glucose are expected. Encephalitis is much more difficult to differentiate. Fever, headache, tremor, ataxia, cranial nerve VI palsy, irritability and lethargic appearance are

findings of encephalitis. CSF findings include increased WBC and protein, normal glucose and negative cultures. In the presented case, fever, altered consciousness, irritability and tremor were present, but the CSF findings were not consistent with meningitis or encephalitis. Although CSF findings may be normal in viral encephalitis at the beginning of the disease, a second CSF analysis performed later in our case was also found to be normal.

Although the exact pathophysiology of NMS is not known, several neuro-mediators including dopamine, serotonin, norepinephrine, gamma-aminobutyric acid (GABA), excitatory amino acid (EAA) and N-methyl-D-aspartate (NMDA) are claimed to play a role in the pathogenesis of the syndrome[5, 22]. Current concepts regarding the pathophysiology of NMS are based on a functional dopamine deficient state triggered by neuroleptic drug-mediated, post-synaptic dopamine receptor blockade and ensuing hyperactivity of excitatory amino acid neurotransmission in the basal ganglia and hypothalamus[5].

Recognition of NMS is the most important therapeutic action for a good outcome, because discontinuation of the causative drug is the first step of the treatment. Other therapeutic measures consist of reducing fever, adequate monitoring, and support of cardiovascular, respiratory, renal and other vital functions. Currently, dopamine agonists such as bromocriptine, amantadine and carbidopa/levodopa and dantrolene are usually administered for the treatment of NMS[7, 23]. Anticholinergics, benzodiazepines and electroconvulsive therapy are often considered to be controversial therapeutic alternatives[7]. However, bromocriptine may exacerbate psychotic symptoms, and dantrolene should be considered as a potentially hepatotoxic drug[23]. Benzodiazepines have been administered to more than 20 patients with transient relief of symptoms in about 40 percent of cases[12]. There are also reports of a beneficial response[23].

We think that our case fulfills the criteria for Stage 3 as discussed by Woodbury and Woodbury[20], and benzodiazepines are among the recommended treatments for this stage[12, 20, 23]. In our case diazepam was also the treatment of choice because of the patient's severe agitation. We observed a rapid recovery of that life-threatening symptom. The remaining features improved relatively slowly. Studies concerning the mode of action of benzodiazepines on NMS argue that this agent may have an indirect dopaminergic effect mediated by GABA-ergic feedback loops within nigrostriatal and mesolimbic centers[24]. Biperiden was also administered in our case for the extrapyramidal symptoms. Although there are various studies suggesting that anticholinergic agents have no effect on NMS, Leikin et al.[25] reported successful results with diphenhydramine. It is known that central dopaminergic blockade in the nigrostriatal pathway causes an excitatory effect on the cholinergic system, which may be responsible for the symptomatology seen in NMS[26]. The effectiveness of biperiden in NMS may be due to its blockade of the cholinergic component of the nigrostriatal pathway.

Another interesting point in our case was the administration of nifedipine to reduce the patient's blood pressure in the local hospital. This agent is reported to be effective in NMS by blocking the neural and muscular calcium channels, which might be involved in the pathophysiology of the syndrome[27]. It can be hypothesized that this agent also had a therapeutic role in our patient, who remained in Stage 3. To avoid unfortunate therapeutic outcomes, we suggest that pediatricians should be sensitive to the possible role of NMS among pediatric patients with fever of unknown origin, striking extrapyramidal symptoms and a recent history of psychopharmacological intervention.

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