8. Rhabdomyolysis and antipsychotics

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Abstract: Drug-induced rhabdomyolysis is not an uncommon syndrome, and its consequences could be lethal. It should be borne in mind that this life-threatening state is a responsibility of all medical experts and should not be underestimated, unnoticed or misdiagnosed. Permanent consciousness, monitoring and early recognition have a pivotal role. Thus, in this paper we will considered some important aspects of rhabdomyolysis and neuroleptic malignant syndrome (NMS) and try to raise an awareness about this intriguing phenomenon throughout possible causes/risk factors, various clinical manifestations, and impact of certain psychopharmacological agents.

Introduction

Most authors agree about the definition of the syndrome of rhabdomyolysis in the sense, that rhabdomyolysis presents destruction or disintegration of
the striated muscle (1, 2). Above mentioned syndrome could be considered as an “urgent condition in medicine”, as it often causes fatal complication and lethal outcome. What further complicates the real clinical situation is that clinical expression of the syndrome may be diverse, ranging from asymptomatic illness to multi-system damage. Rhabdomyolysis is not an uncommon syndrome. In the United States there are about 26,000 cases of rhabdomyolysis per year (3), furthermore 10-50% of patients with rhabdomyolysis develop acute renal failure (ARF) (4), and according to survey performed by Brivet et al. (5) mortality rates are from 7 to 80% out of all patients who develop acute renal failure (ARF).

**Etiology and pathophysiology**

Until now, a numerous causes of rhabdomyolysis have been identified. According to the current data (2, 6-9), causes of rhabdomyolysis could be categorized into hereditary and developed ones, that could be further classified as traumatic and non-traumatic causes (6). Bosch et al. (2) performed a list of “major categories and commonly reported causes of rhabdomyolysis” which include eight categories: “trauma, exertion, muscle hypoxia, genetic deficits, infections, body-temperature changes, metabolic and electrolyte disorders, drugs and toxins, idiopathic”. According to literature (8, 10), genetic causes could be associated with deficiency of certain enzymes, which are necessary in metabolism of lipids, carbohydrates, purines etc. Most frequently reported causes and risk factors for developing rhabdomyolysis are alcohol abuse, muscle overexertion, muscle compression, some medicaments and drugs, electrical shock injury, and crush injury (8, 11-15). From psychiatric point of view, most important for everyday clinical practice are consequences of medication which are used for treatment of those suffering from severe mental illnesses. Wide spectrum of medicaments and drugs could damage muscles, and seriously impair the production or use of ATP by skeletal muscle, finally causing rhabdomyolysis (9, 16). Thus, the recent study of Huerta-Alardín et al. (9) presented a list a drugs which may induce rhabdomyolysis (e.g. haloperidol, lithium, fluoxetine, fluphenazine, chlorpromazine, some sedative hypnotics such as lorazepam, diazepam, nitrazepam, etc). Alcohol, cocaine, D-lysergic acid diethylamide (LSD), sympathomimetics, phencyclidines are also common causes of rhabdomyolysis (17-19) and are important to be mentioned for practitioners who interface on a daily level with the groups of patients who use some of the listed substances.
As we have mentioned above, rhabdomyolysis represents a destruction of skeletal muscles. Despite its numerous causes, there is a characteristic pathogenetic pathway which includes a complex cascade that finally results in release of extracellular calcium ions into the intracellular fluid and circulation (7, 20-21). Myocite destruction, after muscle injury involves a release of intracellular contents into extracellular fluid. The released compounds involve different substances, such as myoglobin, aldolase, potassium, uric acid, lactate dehydrogenase, aspartate transaminase, creatine kinase (CK), phosphate etc. (8,22-23). All these substances, when increased, could have unfavorable effect on different systems and lead to life-threatening situations. Particularly “dangerous” is free myoglobin that could cause potentially fatal renal failure (8).

Clinical manifestations, complications, investigation and treatment

Rhabdomyolysis has a broad spectrum of clinical manifestations, ranging from subclinical to severe. According to Sauret et al. (8), characteristic “local signs and symptoms” could be “muscle pain, tenderness, swelling, weakness“. On the other hand, “systemic features” may involve, “tea-colored urine, fever, malaise, nausea, emesis, altered mental status, anuria“. Furthermore, complications of rhabdomyolysis are also diverse – from early to late (8), from asymptomatic increase in creatine phosphokinase (CK) to serious, life threatening conditions such as ARF, electrolyte imbalance, cardiac arrhythmias, compartmental syndrome, disseminated intravascular coagulopathy (6,24-25) etc. First step in clinical examination is a collection of relevant data (systematic and informative medical record) and physical examination. Also, it is important to bear in mind that some clinical features overlap with other medical conditions (e.g. muscle pain, swelling, weakness), but also that they could be absent. Hence, definitive diagnosis of rhabdomyolysis should be made by sensitive laboratory tests including serum CK, urine myoglobin and finally skeletal muscle biopsy (7). Several authors agree that five-fold increase of CK level(in the nonappearance of heart/brain diseases), could be strong indicator of the diagnosis of rhabdomyolysis (8,26). The most important measures, in cases of rhabdomyolysis, are early identifications of syndrome and prevention of potentially life-threatening complications. Very frequently, these patients need immediate treatment, especially in cases of severe hyperkalemia, ARF, DIC etc. In the most severe cases (e.g. onset of ARF) “aggressive” treatments are necessary and include even hemodialysis (6).
Neuroleptic malignant syndrome as a form of rhabdomyolysis - impact of antipsychotics

Profound exploration of neuroleptic malignant syndrome (NMS) is of great importance for psychiatrists, because this condition belongs to the emergency psychiatric states and needs urgent attention and care. Namely, NMS could be understood as a form of rhabdomyolysis caused by certain drugs which are used in the treatment of neuropsychiatric patients. Although most authors agree that MNS is a rare, but potentially severe, life-threatening complication of the use of the neuroleptics (27-28), it is now known that apart from neuroleptics other drugs pertaining to “psychiatric palettes” could lead to this syndrome (9). According to Keck et al. (29), the frequency of NMS is approximately between 0.02 % to 2.4 %. So far, NMS has been observed in all age categories. Gender proportion is 2:1 in favor of males (30-31). The raising problem for all practitioners, is a deficiency of consensus about criteria for NMS. According to DSM-IV-TR (32), research diagnostic criteria of NMS are: (A) the development of severe muscle rigidity and elevated temperature associated with use of neuroleptic medication. (B) Two (or more) of the following: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, and laboratory evidence of muscle injury (e.g. elevated creatinine phosphokinase). (C) The symptoms in Criteria A and B are not due to another substance (e.g., phencyclidine) or a neurological or other general medical condition (e.g. viral encephalitis). (D) The symptoms in Criteria A and B are not better accounted for by a mental disorder (e.g. mood disorder with catatonic features). Recent study performed by Gurrera et al. (33) which enrolled numerous international experts, raises an initiative to achieve consensus about diagnostic criteria for NMS. This kind of initiative is of great importance for all practitioners, as this syndrome still represents a “hot topic,” in medicine, and our prompt recognition and time appropriate reaction are of vital importance for our patients.

Namely, despite fact that NMS is manly mentioned in the context of adverse reaction of classical antipsychotics, investigators observed this reaction even in the case of atypical antipsychotics (27). Drugs such as antidepressants, antiemetics, anesthetics, and sedatives, which potentially block D2 receptors, could also induce this syndrome (34-37). NMS is dose independent in regard to applied neuroleptics and in most cases develops within the first week of application of neuroleptic agent (31-32, 38-39). It is clinically interesting, that the similar or the same clinical presentation of
NMS have been observed in patients with Parkinson’s disease during treatment with antiparkinsonic drugs (40-41), those who were exposed to drugs with different mechanism of action (e.g. SSRI’s), or surprisingly, those who did not have any pharmacotherapeutic involvement (42-44).

In recent years, investigators’ attention has been focused on atypical antipsychotics - so called “golden standard“ in treatment of severe psychiatric disorders and medications with lower incidence of adverse effect (especially EPS). However, studies observed that even a typical antipsychotics have a potential to induce NMS (27,45). Furthermore, researchers still debate about the most appropriate-or precise name for this syndrome, even an “atypical NMS“(46), but interest should be focused on potentially “non-specific forms”, with atypical presentation observed in case by Ball et al. (47). Study performed by Ananth et al. (45), includes several cases of patients who were exposed to different atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine) in order to explore occurrence of NMS in patients treated by atypical antipsychotics. The source of data was Medline search. They conclude that the mortality rate was lower than that with typical antipsychotic medicaments (for NMS linked with atypical antipsychotics). In that manner, Trollor et al. (27) observed that NMS associated with exposure to atypical antipsychotics presents in a typical way. According to above mentioned review by Trollor et al. (27), clozapine-induced NMS, which appears less associated with EPS. All in all, irrespectively of class of drugs we use in treatment of our patients, neurological side effects are necessary to be carefully monitored. Risk factors such as treatment with high-potency neuroleptics, rapid increase of dose of neuroleptics, parenteral injections of neuroleptics, agitation, high serum CK levels during psychotic episodes etc. are all well documented and already known to increase the risk of developing NMS (48-51). Additionally, it should be borne in mind that complications of NMS are severe and life threatening. Profound autonomic instability, seizures, ARF, DIC, cardiac arrhythmias, sepsis etc. are some of complications that are potentially lethal (31-32, 40, 52-54) and should be early recognized and prevented. Despite that clinical presentation of NMS is well known, it is important to note that it involves hyperpyrexia, extrapyramidal symptoms (usually “lead–pipe“), altered mental status, and autonomic instability, as well as the laboratory finding of an elevated creatine phosphokinase, leukocytosis, myoglobinuria (28,39, 55-57) it is not always easy to differentiate from other states, which could have similar clinical manifestations. Thus, Strawn et al. (58) suggest a wide range of disorders or environmental factors (which include „infections, endocrine disorders, neurological or psychiatric disorders, toxins and medicaments“) that should
be keep in mind in everyday clinical practice, in order to achieve precise diagnostic and therapeutical strategies.

Despite fact that the pathophysiology of NMS is still a topic of debate, dopaminergic blockade on functionally important places, as well as genetic variances of genes that regulate the D<sub>2</sub> receptors are some of possible explanations for this phenomenon (31, 38-39, 55, 59-62). Guidelines for the treatment of NMS are necessary to be considered. The authors agree that initial step is a prompt removal of any drug that has been proven to induce NMS (38-39). After that, supportive therapy is essential (28, 31, 39). There are still controversies about “the most appropriate pharmacological approach”. For example, debate about effectiveness of dantrolene and bromocriptine (63), usefulness of antyholinergics etc. (64). Furthermore, benzodiazepines, as well as, electroconvulsive therapy (ECT), may be helpful for the treatment especially in situations with catatonic presentation (65-67).

**Conclusion**

Drug-induced rhabdomyolysis is not an uncommon syndrome, and its consequences could be lethal. It should be borne in mind that this life-threatening state is a responsibility of all medical experts. Permanent consciousness, monitoring and early recognition have a pivotal role. From the psychiatric point of view, neuroleptic malignant syndrome as a form of rhabdomyolysis, could potentially be induced by neuroleptics and is a state of emergency. Despite that frequency of neurological side effects are less frequent in second generation antipsychotics in comparison to first generation antipsychotics, careful monitoring is not out of place. Finally, this syndrome should not be underestimated, unnoticed or misdiagnosed.

**References**

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The clinical and scientific work of Damjanović predominantly includes research in the field of biological psychiatry (phenomenology of psychotic and affective disorders, targeted and specific pharmacotherapy, genetics, identification of risk factors), with special emphasis on the specific aspects of antipsychotic therapy, and affective disorder. Parallel to these studies, Damjanović focuses his work on the philosophical (bioethical) and cultural elements embedded within psychiatry.