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Case Report

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# Massive Assymptomatic Creatine Kinase Elevation with Quetiapine – A Case Report

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## Abstract

***Context:*** *With the growth of antipsychotic prescription in children and adolescents, it is paramount the adequate monitoring of clinical and analytical parameters. A syndrome of massive creatine kinase elevation has gained attention in the literature in the last decade, with many clinical reports in adults and adolescents with psychotic disorders and under antipsychotic treatment. However, clinical descriptions of this syndrome in adolescents with non-psychotic disorders are still very scarce.*

***Case Report:*** *We describe the clinical case of a 14-year-old girl with a depressive disorder, with no history of psychotropic medication, who developed a massive creatine kinase elevation syndrome upon administration of quetiapine. We explain the diagnostic pathway and the clinical management of the case.*

***Conclusion:*** *This case reflects the need of a greater attention regarding the rare, but clinically relevant syndrome of massive creatine kinase elevation. This recognition will probably lead to a lowering of unnecessary diagnoses of rhabdomyolisis or neuroleptic malignant syndromes in child and adolescent psychiatry practice.*

**Keywords:** Antipsychotic, Quetiapine, Creatine Kinase, Macke syndrome

## Introduction

With the increase of the commonplace use of second generation antipsychotic (SGA)-containing treatment regimens in child and adolescent psychiatry practice, raising concern has arisen regarding the monitoring of their clinical and metabolic effects as well as of more severe adverse events such as the neuroleptic malignant syndrome (NMS). Indeed, there have been some consistent clinical descriptions of a symptomatic and spontaneous elevation of serum creatine kinase (CK) with antipsychotic treatment, apparently not related to NMS, in previously drug-free adults with psychotic disorders [1, 2].

Much less evidence is available on children and adolescents, as there are only few reports of adolescents with schizophrenia who presented high CK levels during SGA treatment [3, 4].

Masi and colleagues have outlined that the described syndrome – Massive Asymptomatic Creatine Kinase Elevation (MACKE) - is an autonomous clinical entity (or a possible side effect) that can occur during antipsychotic drug treatment, in the absence of any additional sign of NMS or rhabdomyolysis, without any progression toward these severe clinical conditions, being self-limiting or reversible after drug discontinuation. In that extensive review, the authors also stated that MACKE can occur during antipsychotic exposure, even in patients without a psychotic disorder and that it is independent of drug type and dosage [5].

Other most frequent reasons for high CK serum levels in psychiatric settings are intramuscular injections, restraints, intense physical activity, dystonic reactions, or other intense isometric activity [6]. High serum CK levels have been also related to over dosage of several substances of abuse, such as cocaine and amphetamines, including "ecstasy" [7]. Among medical conditions resulting in CK elevations, myocardial infarction, thyroid dysfunctions, and muscle injuries or syndromes are all possible causes of CK elevation. Moghadam-Kia and colleagues have recently summarized a useful clinical workup and differential diagnosis in the presence of idiopathic CK elevation [8].

We hereby present the clinical case of a patient with a clinical picture compatible with MACKE syndrome after the administration of oral quetiapine.

## Case Presentation

Ms. I. is a fourteen-year-old female Caucasian adolescent. She was admitted to the child and adolescent psychiatry ward with a depressive disorder with suicidal ideation. There was no relevant past medical history, including no history of any psychotropic medication. Upon entry into our unit, she presented clinically relevant insomnia and 50mg of long-acting quetiapine was administered per os once daily. On day 3 after admission a massive serum CK elevation (levels 6 times above the superior limit of normal) was detected with normal AST and ALT. The patient was extensively assessed and remained always asymptomatic regarding fever, pain, weakness, muscle stiffness or any other physical or neurological symptoms.

There was no history of drug consumption or compatible physical activity. The quetiapine was suspended and fluid therapy was initiated. On day 6 after admission serum CK continued to rise until levels 40 times the superior limit of normal, with no symptoms suggestive of NMS or rabdomyolysis. She was then reassessed by a pediatrician and a child neurologist confirming absence of suggestive symptoms. In the clinical workup performed - Electrocardiogram, echocardiogram, whole body magnetic resonance, pregnancy test, serum myoglobin, CK-MB, troponin, hemogram, ionogram, viral serologies, serum acylcarnitines and lactate, CRP and ESR – no abnormalities were found. During the following week the serum CK levels have shown a descending profile until normal values. The clinical picture is, therefore, highly suggestive of a quetiapine-induced MACKE syndrome in a non-psychotic adolescent.

## Discussion

This is, to our knowledge, the first clinical report of a non-psychotic female adolescent with no psychotropic drug history presenting MACKE syndrome associated with quetiapine. Although we did not have any baseline level of serum CK, the lowering after quetiapine withdrawal suggests a causal relationship.

When in the presence of such CK elevations a strict monitoring protocol is advised, particularly when it comes to the clinical distinction from NMS and rhabdomyolisis. Table 1 summarizes the clinical symptoms and findings that may help in differential diagnosis. One must also bear in mind that serum CK levels are strongly affected by race, sex, and physical activity. A patient with truly elevated levels should be evaluated for a variety of non-neuromuscular causes, including endocrine disorders, metabolic disturbances, drug effects, and malignancy.

**Table 1: Clinical parameters relevant for the main differential diagnosis of MACKE**

| Symptoms | NMS | Rhabdomyolysis | MACKE |
|---|---|---|---|
| Hyperthermia | + | ++ / - | - |
| Muscle Stiffness | + | - | - |
| Autonomical Instability | + | - | - |
| ↑Heart Rate | ++ / - | + / - | - |
| ↑Blood Pressure | ++ / - | + / - | - |
| Altered Consciousness | + | - | - |
| CK elevation | ++ / - | + / - | + |
| Myalgia | - | + | - |
| Weakness | - | + | - |
| Coluria | - | + | - |
| Myoglobinuria | + / - | + / - | - |
| ↑Transaminases | + / - | + / - | + / - |
| ↑Serum Potassium | - | ++ / - | - |

+ present in all cases
- almost never present
++ / - present in almost all cases, depending upon degree of severity
+ / - can be present or not

With the finding of MACKE, the issue is how to balance a cost/benefit evaluation. Our clinical vignette is an example of a use of probably unnecessary diagnostic testing that is not practical or useful on a large scale level. Furthermore, an unnecessary discontinuation of an effective treatment may lead to greater burden and clinical worsening of such patients. Indeed, dose reduction or discontinuation is only advised in cases with massive (i.e. above 5000U/L) or persistent (i.e. with more than 2 weeks) serum CK elevations [5].

Due to the apparently benign and self-limited clinical course, a "wait and see" approach with close clinical monitoring is advised, with judicious use of ancillary diagnostic testing. The prompt recognition and increasing awareness about MACKE will add to its clinical characterization and contribute to the potential discovery of its pathophysiological mechanisms.

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