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CASE REPORT

Neuroleptic malignant syndrome in an adolescent with the GNAO1 mutation movement disorder phenotype: a challenging diagnosis

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Abstract

Introduction: Neuroleptic malignant syndrome (NMS) is a rare and life-threatening condition resulting from exposure to dopamine-blocking agents. GNAO1 mutations are a neurodevelopmental disorder associated with a hyperkinetic movement disorder, usually treated with dopamine-blocking agents. **Case report:** A 16-year-old adolescent, previously diagnosed with a GNAO1 dyskinetic movement disorder, and prescribed tetrabenazine, chlorpromazine and clonidine, was admitted during the summer due to nausea, fever and a slight worsening of dyskinesias. Initially, a heat stroke was assumed. A few days later, the patient manifested generalized dyskinesias, refractory hyperthermia, diaphoresis and progressive worsening of consciousness, suggesting neuroleptic malignant syndrome. Neuroleptic treatment was stopped, and the patient was started on dantrolene and admitted to the pediatric intensive care unit. The patient eventually recovered over the subsequent two months, symptomatic treatment for dyskinesias was slowly introduced, except chlorpromazine, and he was admitted to a rehabilitation center. **Discussion:** This case illustrates the diagnostic challenge of malignant neuroleptic syndrome in children and adolescents, particularly in patients with previous dyskinetic movement disorders treated with dopamine antagonists.

Síndrome neuroléptica maligna em um adolescente com fenótipo de transtorno do movimento por mutação GNAO1: um diagnóstico desafiador

Resumo

Introdução: O síndrome maligno dos neurolépticos é uma entidade grave, associada ao uso de agentes antidopaminérgicos. Mutações no gene GNAO1 podem manifestarse por doenças do movimento hipercinéticas, frequentemente tratadas com agentes antidopaminérgicos. **Relato do caso:** Um adolescente de 16 anos, com antecedentes de doença do movimento associada a mutação no gene GNAO1, tratado com tetrabenazina, clorpromazina e clodina, foi admitido no verão por náusea, febre e agravamento de discinesias. Inicialmente, foi assumido o diagnóstico de golpe de calor. Dias depois, apresentou discinesias generalizadas, hipertermia refratária, diaforese e agravamento progressivo do estado de consciência, sugerindo um síndrome maligno dos neurolépticos. Os fármacos neurolépticos foram suspensos, foi iniciado dantroleno e o doente foi

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transferido para a unidade de cuidados intensivos pediátricos. Verificou-se recuperação progressiva em dois meses, e a medicação de ambulatório foi lentamente introduzida, exceto a clorpromazina. **Discussão:** Este caso ilustra o desafio do diagnóstico de síndrome maligno dos neurolépticos em idade pediátrica, particularmente em doentes com antecedentes de doenças do movimento hipercinéticas tratadas com antagonistas dopaminérgicos.

Palavras-chave: Síndrome maligno dos neurolépticos. Mutação GNAO1. Doença do movimento.

Keypoints

What is known
- Neuroleptic malignant syndrome is a rare and life-threatening condition associated with exposure to dopamine-blocking agents.
- It manifests itself with severe extrapyramidal symptoms, an altered level of consciousness, fever, dysautonomia, rhabdomyolysis and potential multiple organ failure.
- Early diagnosis and treatment are crucial to improve prognosis.

What is new
- Patients on dopamine-blocking agents are more susceptible to both heat stroke and NMS.
- In patients with a previous history of movement disorders and pre-existing extrapyramidal symptoms, a high level of suspicion is required to diagnose NMS.

Introduction

Neuroleptic malignant syndrome (NMS) is a rare, yet life-threatening condition. It was first defined in the late 1950s[1], and the term was originally used to describe potentially severe extrapyramidal symptoms as side effects of first-generation antipsychotic drugs. It is now known that even atypical dopamine antagonists and the withdrawal of dopamine agonists and mood stabilizers are alternative causes. The main risk factor for developing NMS is the initiation or increase in the dosage of dopamine-blocking agents[2].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) includes exposure to dopamine-blocking agents, severe muscle rigidity and fever as major diagnostic criteria. Other features are an altered level of consciousness, tremor, dysphagia, dysautonomia, leukocytosis and elevated creatine phosphokinase[3]. Complications include rhabdomyolysis, renal and respiratory failure, sepsis and death (mortality rate 5.6%). Emergency treatment is required, with the prompt cessation of causative agents and the initiation of supportive therapy and benzodiazepines. Globally, the prevalence of NMS is now lower (0.01 – 0.02%) as a result of attention to the prescription and titration of these drugs[4].

We report the occurrence of NMS in a male adolescent diagnosed with GNAO1 mutation with a hyperkinetic movement disorder. This is a challenging diagnosis in children with movement disorders given the low incidence and the pre-existence of extrapyramidal symptoms.

Case report

On a hot August afternoon, a 16-year-old adolescent was admitted to the emergency department due to feeling unwell, nauseated and refusing to eat after being at the beach with his family during the day. He had been diagnosed with GNAO1 encephalopathy at the age of 12 (confirmed by genetic testing), presenting with global development delay, dystonia and chorea since his first year of life. The brain magnetic resonance imaging (MRI) and metabolic testing were normal. Following several episodes of status dystonicus requiring hospital admission in the ICU, he was submitted to bilateral deep brain stimulation of the internal globus pallidus (GPi DBS) when he was 13 years old, with significant improvement. Before the event in question, the patient was partially dependent for daily routine activities, but capable of autonomous gait. He had dysarthric but fluent speech, and had oral, trunk and limb dystonia, controlled with tetrabenazine 18.75 mg daily (TID), chlorpromazine 37.5 mg daily (TID) and clonidine 0.33 mg daily (TID). There had been no recent changes to medication.

When the patient first arrived at the hospital, his temperature was 40.7 °C, while other vital signs and his blood glucose levels were normal. Besides a slight worsening of upper limp dyskinesias controlled with diazepam, the neurological examination presented no additional remarks. Blood tests in the first 12 hours of admission showed significant leukocytosis (35400 x 10^9 cells/L), elevated creatine phosphokinase (CK) (87250 U/L), and acute renal failure (creatinine 1.61 mg/dL). The

patient was admitted to the Pediatric Neurology department with the hypothesis of a heat stroke and secondary rhabdomyolysis and acute renal failure. Aggressive hydration was started, as well as diuresis monitoring through bladder catheterization.

In the first five days of hospital admission, he was apyretic and showed a significant clinical recovery. His renal function was normal and CK levels were consistently decreasing (21747 U/L). Fever and dysuria then ensued, with elevated inflammatory parameters, suggesting a urinary tract infection in the context of recent bladder catheterization. He was started on empiric antibiotic therapy with amoxicillin and clavulanic acid. The next day, severe generalized dyskinesia followed, and symptomatic treatment with oral and intravenous diazepam 5 mg and intravenous chlorpromazine 25 mg was administered. However, at the end of the day he deteriorated to the point of refractory hyperthermia, tachycardia, diaphoresis and a progressive decline in consciousness (Glasgow Coma Scale 9 – O2V2M5). His blood pressure and cardiac rhythm were normal and he showed no muscle rigidity. Deep brain stimulation (DBS) was functioning correctly. At this point, CK levels were rising again (80550 U/L) and neuroleptic malignant syndrome was suspected. Chlorpromazine and tetrabenazine were immediately stopped, hydration therapy was intensified, diazepam was continued and he was started on dantrolene 140 mg.

The patient was admitted to the pediatric intensive care unit (ICU) given the systemic multiple organ failure and distributive shock. His CK levels reached over 600000 U/L during his admission to the ICU, where he stayed for 26 days. The patient needed respiratory support through mechanical ventilation for 13 days, kidney function support through ultrafiltration for 18 days and cardiac support with vasoactive drugs during his initial days of admission. On the 20th day, following an acute decline in consciousness, the brain MRI showed bilateral occipital parenchymal hemorrhage suggestive of posterior reversible encephalopathy syndrome (Fig. 1) because of uncontrolled hypertension (probably the consequence of acute renal failure), which was then treated with labetalol and minoxidil. Concomitant respiratory infections were also diagnosed and treated.

After one month in the ICU, cardiac, respiratory and renal function returned to normal, as did his CK levels. Following progressive improvement in consciousness, the dyskinesias worsened. In the acute setting, dyskinesias were first controlled by adjusting sedative therapy (midazolam, fentanyl and ketamine). Clonidine was then restarted (first intravenously, max. 2 mcg/kg/h and then orally, max. 300 mcg every four hours). Other drugs were needed during the subacute phase to control dyskinesias, namely diazepam (max. 10 mg, TID), topiramate (max. 50 mg, BID), baclofen (max. 20 mg, TID) and trihexyphenidyl (max. 1 mg, TID). DBS parameters were also adjusted.

Two months later, the patient was discharged after an adjustment to his medication, communicating through mime and simple words. He had left-sided homonymous hemianopsia, generalized muscle atrophy and moderate tetraparesis, and also sporadic oral dyskinesias and left hand dystonia. Tetrabenazine was then slowly introduced in the clinic to better control dystonia, but chlorpromazine was not restarted. One year later, he recovered independent gait and speech, and the patient is now stable under tetrabenazine 37.5 mg per day, clonidine 1.8 mg per day (QID) and DBS stimulation.

Discussion

We present a challenging diagnosis of neuroleptic malignant syndrome. The first episode that brought the patient to the emergency room makes us wonder whether this was already the insidious start of NMS or in fact a heat stroke. These two entities share common features, such as hyperthermia, central nervous system dysfunction, dysautonomia, rhabdomyolysis and a potentially poor prognosis with intensive care admission. Heat stroke may also be facilitated in patients taking antipsychotic drugs, as the blockage of hypothalamic thermoregulatory pathways inhibits heat dissipation[5,6]. Another possibility to be considered, given the previous history of status dystonicus, would be a dystonic storm in the event of sudden DBS failure[7]. However, DBS was confirmed to be functioning correctly.

This episode occurred during a very hot summer day, during which the patient refused to eat and drink, leading to dehydration. There had been no changes to his antipsychotic medication in the last few months, and the patient improved after hydration alone and a slight increase in the benzodiazepine dosage on demand, without the need to stop regular medication. This suggests that the first episode was a heat stroke. Although there is no widely accepted definition for this, Bouchama's definition describes exposure to environmental heat, a core body temperature of > 40 °C and organ dysfunction (central nervous system, liver, renal, cardiovascular or respiratory).

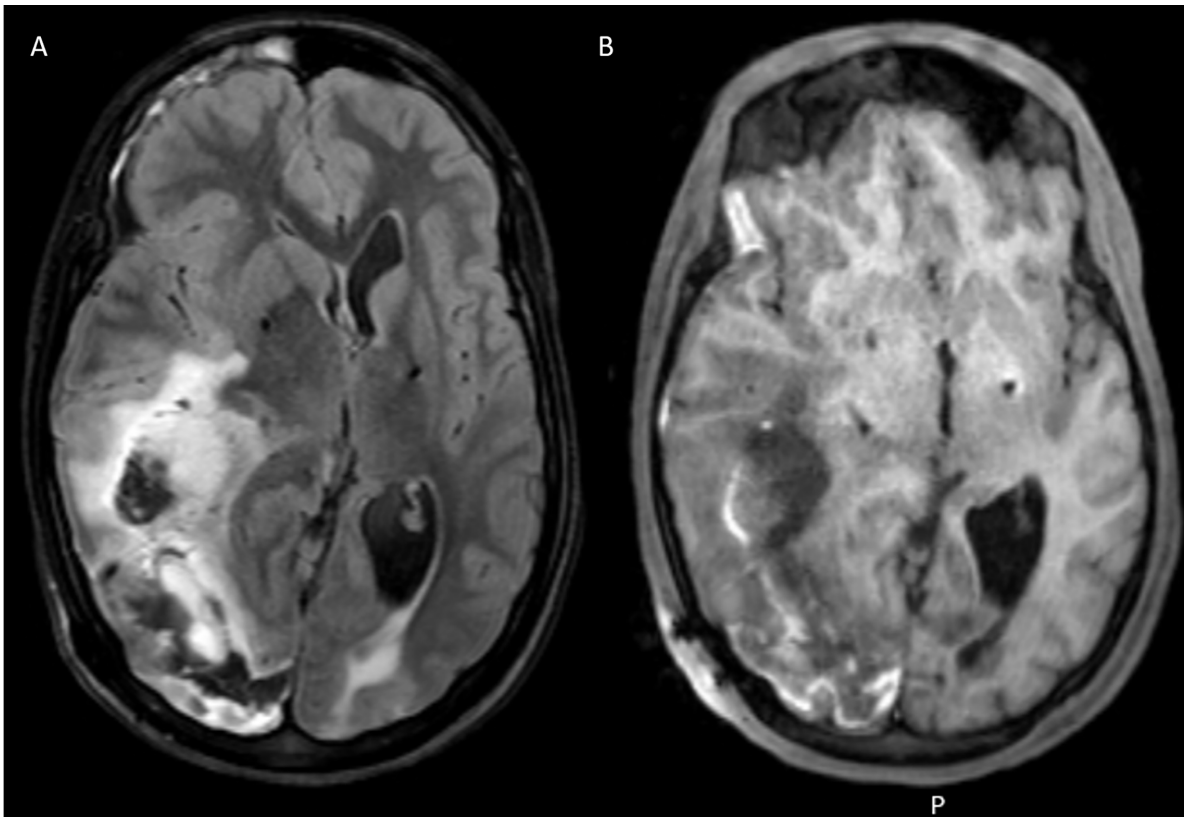

Figure 1. Brain magnetic resonance imaging showing (**A**) bilateral occipital T2 FLAIR subcortical hyperintensities, particularly on the right, (**B**) with T1 peripheral gadolinium enhancement and hemorrhage, causing subfalcine herniation, compatible with posterior reversible encephalopathy syndrome.

After a transient clinical improvement, fever and dysuria ensued in the context of a post-catheterization bladder infection. The baseline dyskinesia became more frequent, and the symptomatic medication dosage was increased (benzodiazepine and chlorpromazine). We hypothesized that this was the moment NMS ensued, as it most frequently occurs within two weeks after drug initiation or an increase in the dosage[1]. However, NMS is ultimately an idiosyncratic reaction and has been known to occur in patients who have been stable on medication for years[8]. Besides chlorpromazine, the patient was also medicated with tetrabenazine, which has also been associated with NMS[9].

Movement disorders are known to be a feature of NMS. However, in this case, they were first interpreted as neurological worsening secondary to heat stroke, dehydration and infection. In this particular subgroup of movement disorders, a high level of suspicion is needed to detect NMS. Pediatric patients are also more susceptible to side effects related to antipsychotic drugs, even in lower doses[10].

Nonetheless, few studies exist regarding NMS in children and adolescents. A recent review of case reports[1] identified 57 pediatric patients diagnosed with NMS between 2000 and 2018. The mean age was 14 years, most patients were male and 49/57 had psychiatric comorbidities requiring antipsychotic treatment. The most common symptoms were muscle rigidity, autonomic instability and fever. Abnormal involuntary movements were more frequently associated with classical antipsychotic drugs, such as chlorpromazine.

In these patients, after managing the acute period, long-term treatment also presents a challenge, as chorea may become refractory after stopping the worst-offending drugs. In our case, even with DBS parameter adjustments, dyskinesia became very frequent while sedation was decreased. Clonidine was the first drug to be reintroduced since it was less likely to cause NMS and more likely to have a beneficial effect in controlling the dysautonomia in this syndrome. Tetrabenazine was later introduced during clinical follow-up, but chlorpromazine was not restarted given its stronger association

with NMS. A case report in the literature describes a woman with a GNAO1 mutation who developed NMS induced by tiapride and haloperidol[11], who was then successfully treated with topiramate as a safe alternative. In the subacute/rehabilitation phase, diazepam, topiramate, baclofen and trihexyphenidyl were needed to achieve symptomatic control.

In conclusion, our case highlights the difficulty of diagnosing malignant neuroleptic syndrome in an adolescent with previous movement disorder diagnosis. It also illustrates the overlap between heat stroke and NMS in these patients. Close monitoring by a multidisciplinary team consisting of a neurologist, pediatrician and intensivist is essential to avoid unfavorable outcomes. Although rare, the use of clinical protocols and algorithms when NMS is suspected, could be helpful in the therapeutic management of these patients.

Author contributions

M. Santos: Writing – Original Draft, Investigation. T. Proença dos Santos: Resources, Investigation, Writing – Review & Editing. S. Almeida: Resources, Investigation, Writing – Review & Editing. M. Coelho: Resources, Investigation, Writing - Review & Editing. A. Levy: Writing – Review & Editing, Supervision.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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