Levodopa Withdrawal in Parkinson's Disease: a Rare Cause of Fever Necessitating Intensive Care

Yoğun Bakım Gerektiren Nadir Bir Ateş Nedeni: Parkinson Hastalığında Levodopa Çekilmesi

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Abstract

Malignant syndrome (MS) is a condition characterized by hyperthermia, rigidity, high creatine kinase levels and autonomic dysfunction (tachycardia, perspiration, non-obstructive ileus, arterial blood pressure fluctuation, vocal cord paralysis) and is due to decreased dopamine content or inhibition of the dopaminergic receptors in the brain. Mortality is mainly due to severe complications.The differential diagnosis of MS in a patient with Parkinson's disease who was admitted with high fever and impaired consciousness is discussed. Higher than normal weather temperatures, dehydration and uncompliance to medications to medications were accepted as the triggering factors for MS. After admission, acute renal failure and acute respiratory distress syndrome developed; normothermia, improvement of renal functions and consciousness were achieved with levodopa treatment and supportive therapy. In conclusion, hyperthermia, rigidity and impaired consciousness in a patient with Parkinson's disease should be evaluated for MS and dopamine replacement therapy should be administered promptly to avoid severe complications. Antiparkinsonian drugs should be continued in patients with Parkinson's disease admitted due to other problems. (Yoğun Bakım Derg 2010; 2: 52-4)

Key words: Malignant syndrome, hyperthermia, rhabdomyolysis

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Özet

Malign sendrom (MS); hipertermi, kas rijiditesi, yüksek kreatin kinaz düzeyleri ve otonomik disfonksiyon ile seyreden; beyinde dopamin içeriğinin azalması ya da dopamin reseptörlerinin blokajı sonucu gelişen bir durumdur. Mortalite ciddi komplikasyonları nedeniyle görülebilmektedir. Bu yazıda yüksek ateş ve bilinç bulanıklığı ile yoğun bakım ünitesine kabul edilen bir Parkinson hastasında MS tanısı tartışılmaktadır. Hastanın yattığı dönemdeki mevsim normalleri üzerindeki sıcaklar, dehidratasyon ve son günlerde ilaçlarını kullanmamış olması MS'i tetikleyen faktörler olarak kabul edilmiştir. İzlemde akut böbrek yetmezliği ve akut solunum sıkıntısı sendromu gelişmiş; destek tedavilerin yanı sıra başlanan levodopa tedavisi sonrası normotermiye ulaşılmış, renal işlevleri düzelmiş ve bilinç durumu iyileşmiştir. Özetle, Parkinson hastalığı seyrinde hipertermi, rijidite ve bilinç bulanıklığı gelişmesi durumunda MS'den şüphelenilmesi, ciddi komplikasyonların önlenebilmesi amacıyla en kısa zamanda dopaminerjik replasman tedavisine başlanması ve farklı nedenlerle hastane yatışı gereken Parkinson hastalarında antiparkinson ilaçların kesilmemesi önerilmektedir.
(Yoğun Bakım Derg 2010; 2: 52-4)

Anahtar sözcükler: Malign sendrom, hipertermi, rabdomiyoliz

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Malignant syndrome (MS) in Parkinson's disease is a potentially lethal condition and is characterized with high fever, rigidity, disturbance of consciousness, autonomic dysfunction (tachycardia, perspiration, non-obstructive ileus, arterial arterial blood pressure fluctuation, vocal cord paralysis) and elevation of creatine kinase (1). Rhabdomyolysis, aspiration pneumonia, disseminated intravascular coagulation and acute renal failure due to massive rhabdomyolysis induced pigment nephropathy are serious complications which can be lethal unless an early diagnosis and prompt treatment is achieved.

Fever of non-infectious cause is often a challenging problem for most clinicians and intensive care physicians also. In intensive care units (ICU), patients with FUO should be evaluated for malignancies, autoimmune conditions and other miscellaneous etiologies. Here we report a patient with Parkinson's disease (PD) who presented with fever and was evaluated for possible causes of fever. We aimed to discuss possible non-infectious causes of fever in ICU, malignant syndrome as a possible cause of fever in ICU, the importance of this clinical condition, and treatment strategies of this condition.

Case

A 64 year old man with PD presented with high grade fever for 1 week that reached 39.2°C and accompanying disturbance of consciousness. Ten days before admission he had fallen from bed and had suffered minor trauma to his head. After a couple of days his consciousness was disturbed and he progressively became unaware of his surroundings. On his admission to the emergency service, the neurological examination revealed disorientation, no focal deficit but marked rigidity. He had abdominal discomfort and tenderness. Laboratory results showed hyponatremia (124 mEq/L), hypophosphatemia (1,7 mg/dL) and leukocytosis (18,000/mL). A cranial CT was performed and revealed no pathology other than senile cerebral atrophy. Abdominal ultrasonography was

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unrevealing, and functional ileus was the primary diagnosis for abdominal tenderness. Since he had not had an adequate oral intake for the previous ten days and the weather was hot (around 39°C-40°C); hypovolemia and dehydration were considered to be the cause of hyponatremia and subsequent impaired consciousness. After administration of hypertonic saline solution, sodium levels increased to 130 mEq/L in 24 hours. However, his consciousness did not improve even after normalization of serum sodium. He was admitted to the ICU for further diagnostic evaluation and treatment 24 hours after admission to the emergency department and was intubated due to his deteriorating consciousness. Fever and altered consciousness raised suspicion of a central nervous system infection, so a lumbar puncture was done, but results were unrevealing. Physical examination revealed ongoing abdominal tenderness. Since he had fever that rose to 41°C, together with leukocytosis, an intraabdominal infection was investigated. Abdominal ultrasound was performed. No intraabdominal free fluid, abscess or collection was detected. Functional ileus was considered as a possible diagnosis. Nasogastric aspiration, digital rectal examination and rectal enema were performed, then the functional ileus resolved. Other sources of fever were investigated but there was no cause of fever; chest X ray, urine analysis and cultures, stool cultures etc. were unrevealing. Fever was unresponsive to antipyretics (paracetamol and naproxen sodium). To exclude other possible causes of fever and impaired consciousness, autoimmune markers ANA, anti-ds DNA and Brucella agglutination were studied but were negative. On the following days he had no response to painful stimuli. During his stay in the ICU a new onset atrial fibrillation was treated with amiodarone infusion and electrical cardioversion.

During his stay in ICU, he became oliguric and urea and creatinine levels increased. Creatine kinase and myoglobin levels were found to be high (Creatine kinase >10,000 IU/mL, myoglobin >2500 IU/mL), which was compatible with rhabdomyolysis. Acute renal failure (ARF) developed. To rule out a posible structural pathology for renal failure; a renal ultrasound was done and was unrevealing. Renal replacement therapy with hemodialysis was started for acute renal failure.

He was diagnosed with PD about a year earlier. A review of the past medical history with his relatives on admission to the ICU revealed that he had not taken levodopa for about two weeks, taking in account the time spent in the emergency department, malignant syndrome due to levodopa withdrawal was considered as a probable diagnosis which could explain the whole clinical picture. Levodopa treatment was promptly initiated.

Levodopa treatment was followed by normothermia within a few days. However,his consciousness did not improve at this period. Cranial MRI was performed to exclude other organic causes of disturbed consciousness, which showed cerebral atrophy and chronic ischemic changes. During the 8th day of stay in ICU, acute respiratory distress syndrome developed with accompanying fever after aspiration of gastric contents during an endotracheal tube exchange for a leaking cuff. Subsequently he developed ventilator associated pneumonia (VAP) caused by *Acinetobacter baumanii* and *Escherichia coli*. Normothermia was achieved after two days of antibiotic therapy with netilmycin, sulbactam and cefoperazone. Gradual improvement of renal functions was followed by gradual improvement in the consciousness level. Ten days after beginning levodopa treatment we observed he could open his eyes in response to verbal stimuli. The need for dialysis decreased gradually and ended as creatinine levels returned to normal limits. The patient's overall condition gradually improved and he was discharged home in good health.

Discussion

Fever in adults is defined as a temperature higher than 38.3°C (100.9°F) (2). About one third is caused by infections, followed by neoplasms and noninfectious inflammatory conditions. Some other common non-infectious causes may be endocrine problems, hematomas, infarcts and drug fevers. Some may still remain undiagnosed despite vigorous investigation. For the differential diagnosis, a careful review of history and physical examination should be performed and relevant laboratory studies should be planned. In the ICU, non-infectious causes of fever are as common as infectious causes and a very meticulous evaluation should be performed to avoid delay of antibiotic therapy in emergency cases such as meningitis, while minimizing unnecessary administration of antibiotics and looking for other possibly fatal but non-infectious causes of fever. Careful review of the past medical history including past medications can be surprisingly rewarding, although it is commonly seen as a burden and time loss by the ICU staff and the family members, who are concerned for the present condition of the patient.

Hyperthermia is the result of uncontrolled increase in body temperature with an inability to lose heat (2). It is commonly unresponsive to antipyretics and can be fatal. Heat stroke, drug induced hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia, some endocrinopathies and central nervous system damage may present as hyperthermia (2). Of these, MS in Parkinson's disease is a rare condition, caused by decreased dopamine content or inhibition of the dopaminergic receptors in the central nervous system, mainly the hypothalamus and the nigrostriatal system (3). Although the pathogenesis is not yet clear, autonomic dysfunction and hypermetabolism of the skeletal muscles are also suggested to be contributing factors. As a result, heat production is increased. Many drugs, including antipsychotic phenothiazines, some antidepressants and metoclopramide can be the cause, while withdrawal of the dopaminergic agents can also precipitate the syndrome (2).

PD is the result of progressive dysfunction of dopaminergic transmission in the basal ganglia and is treated with a dopamine precursor leveodopa. MS in PD is a relatively rare condition; it is seen roughly in 2-3% of patients (1). It is characterized with hyperthermia (unresponsive to antipyretics), rigidity, worsening of parkinsonism, disturbance of consciousness, autonomic dysfunction (tachycardia, perspiration, paralytic ileus, fluctuation of blood pressure, vocal cord paralysis) and elevation of serum creatine kinase (Table 1). Fever is the most common presenting symptom (1). Although our patient had fever on admission, the previous history of head trauma and disturbance of consciousness raised suspicion of menengitis or epidural or subdural hematoma at first as possible causes of fever. MS should be kept in mind in patients with PD presenting with high grade fever since early diagnosis and prompt treatment is necessary and early diagnosis relies on clinical suspicion.

Table 1. Symptoms and signs of malignant syndrome in Parkinson's disease

High temperature (>38˚C)
Muscle rigidity
Altered mentation
Rhabdomyolysis
Autonomic dysfunction
Tachycardia, paralytic ileus, urinary retention, anhydrosis
High levels of creatine kinase
Disseminated intravascular coagulopathy
Acute renal failure (due to myoglobinuria)
Disseminated intravascular coagulation

In MS in PD, the triggering event is most often discontinuation or dose reduction of antiparkinsonian drugs particularly of levodopa, such as in our case (Table 2). Other precipitating factors may be poor compliance, poor absorption of levodopa (ileus, continuous enteral feeding), intercurrent infections such as pneumonia or urinary tract infections, and dehydration in hot weather (3). Our patient presented after a particularly hot week in summer. One interesting point was that our patient had the shortest duration of PD compared to other cases reported to have developed MS. We know that compliance to medications, especially in chronic diseases, decrease as time passes. This may explain why most of MS patients reported in the literature had a longer duration of illnesses.

Malignant syndrome has a mortality rate of 4% but it is a curable condition (1). Mortality is mainly due to serious complications such as ARF due to rhabdomyolysis, acute hepatic failure, acute heart failure, acute myocardial infarction, disseminated intravascular coagulation, aspiration pneumonia, sepsis and seizures. Treatment is mainly supportive, and consists of intravenous hydration, external cooling, levodopa repletion and the treatment of complications such as hemodialysis for ARF, antibiotics for concurrent infections, and treatment for disseminated intravascular coagulation (Table 3) (3, 4). Intravenous hydration is of utmost importance, since patients may be dehydrated at presentation and additional losses may occur because of autonomic dysfunction induced severe perspiration and diarrhea. Electrolytes should be replenished and glucose and vitamin supplementation be given. Nutritional support should be considered if the patient is unable to eat. External cooling should be started with ice packs. Levodopa replacement should be resumed at prior treatment doses. Bromocriptine can also be used as a dopamine agonist, although there are no controlled studies (3, 4). Dantrolene sodium, which inhibits calcium release by the sarcoplasmic reticulum and is used commonly for malignant hyperthermia, is recommended also in the setting of MS (3, 4). Other drugs used in the literature include amantadine and pulse steroids although there are no large controlled studies to support their routine clinical use in MS (5 ,6). In our case prompt treatment with levodopa was started and normothermia was achieved thereafter, improvement of renal function followed this, with a slower improvement in consciousness level. It is important that the treatment should be followed in the ICU until the life threatening complications are under control.

In conclusion if a patient with PD develops hyperthermia, rigidity and impaired consciousness, MS should be suspected and dopaminergic replacement should be restarted as soon as possible to prevent serious complications. Also if a patient with PD is hospitalized for another medical problem, the antiparkinsonian medications should not be discontinued unless there is a contraindication. Even then, dose reduction should be made gradually under close supervision.

Table 2. Triggering factors for malignant syndrome in Parkinson's disease

Drug discontinuation/ dose reduction
Noncompliance to medication
Infection
Dehydration
Drug wearing-off

Table 3. Treatment of malignant syndrome in Parkinson's disease

Intravenous hydration
Cooling
Start of dopaminergic drugs: levodopa, bromocriptine
Pre-event doses should be resumed orally or by N/G tube
Dantrolene sodium (there are no controlled studies)
Antibiotics (if there is concurrent infection)
Prophylaxis/ Treatment of complications
Renal replacement therapies
Treatment of disseminated intravascular coagulation
Mechanical ventilation
Nutrition support (orally or by enteral route if possible)

Conflict of Interest

No conflict of interest is declared by authors.

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