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Cese Report / *Olgu Sunumu*

Malignant Syndrome in a Patient with Parkinson's Disease

Parkinson Hastalığı Olan Bir Olguda Malign Sendrom

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Summary

Malignant syndrome during the course of Parkinson's disease usually results from withdrawal or dose reduction of anti-Parkinsonian drugs, especially levodopa, and may be fatal. Major clinical findings are fever, rigidity, autonomic dysfunction, elevated creatinine kinase levels and confusion. We present a patient who was treated in our intensive care unit to emphasize the importance of correct diagnosis, to discuss precipitating factors and to highlight the importance of early treatment. *(Turkish Journal of Neurology 2012; 18:123-5)*

Key Words: Parkinson's disease, malignant syndrome, levodopa, infection

Özet

Malign sendrom Parkinson hastalığının seyrinde anti-Parkinson ilaçların, özellikle levodopanın ani olarak kesilmesi veya doz azaltılması sonucu görülmektedir ve fatal seyirli olabilen bir hastalıktır. Ateş, rijidite, otonomik disfonksiyon, kreatinin kinaz seviyesinde artış ve bilinç bulanıklığı temel klinik bulgularıdır. Biz de bu hastalıkta teşhisi doğru koymak, presipitan faktörleri tartışmak ve tedaviye erken başlamanın önemini vurgulamak için yoğun bakımımızda tedavi edilen bir olguyu sunmayı amaçladık. *(Türk Nöroloji Dergisi 2012; 18:123-5)*

Anahtar Kelimeler: Parkinson hastalığı, malign sendrom, levodopa, enfeksiyon

Introduction

Malignant syndrome (MS) is a disorder seen as a result of the sudden discontinuation or dose decrease of anti-parkinson drugs, especially levodopa, in the course of Parkinson's disease (PD) (1,2). This syndrome presents with a clinical picture very similar to neuroleptic malignant syndrome (NMS) resulting from the use of typical neuroleptic drugs, although the underlying condition is different (3). Body temperature may rise to 40°C but may also be rarely normal. There are evident cases of rigidity, changes in consciousness and autonomic dysfunction signs. The most important laboratory finding in MS is a severe increase in serum creatinine kinase (CK) level due to massive rhabdomyolysis (4,5). Early diagnosis and treatment may prevent the development of complications. Most common complications are disseminated intravascular coagulation, aspiration pneumonia and acute renal failure with a mortality rate of 4% (4). We present a patient whose general condition worsened due to an intervening pulmonary infection while under treatment for PD; treatment was discontinued, which led to the development of MS, and the patient died as a result of hospital infection and acute renal failure.

Case

A 56-year old male patient, under control with a diagnosis of PD for 5 years, had been using levodopa 465 mg/day and

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amantadine 300 mg/day. He took a fall three times 15 day prior to presenting at our hospital. The lumbar x-ray and computerized brain tomography was found to be normal at the clinic he went after the fall. His body temperature, which was 37°C at that time rose in ten days and the patient went to the emergency room. No pathology was found in his complete blood count, urinalysis and chest x-ray. His fatigue and anorexia increased daily, and his drugs were withheld for 3 days, at the end of which his general condition worsened, his fever rose to 40°C and he returned to the emergency room. As he had respiratory distress, he was intubated and admitted in the intensive care unit of our hospital.

The patient was unconscious during the neurologic examination performed immediately after being admitted in the intensive care unit. There was clear rigidity in all extremities and especially neck muscles. His blood pressure was 190/100 mmHg and heart rate was 150/min. Serum CK was 4265 U/L. CK-MB value was normal and troponin-T value was negative. Aspartate aminotransferase (AST) was 154 U/L, alanine aminotransferase (ALT) was 50 U/L, C-reactive protein was 155 mg/L and procalcitonin value was 70 ng/mL. Central venous pressure values were +6, +8 and +12 on the first day, second day, and third day, respectively. Treatment was initiated with fluid replacement and antipyretic drugs. Levodopa 1000 mg/day was administered via nasogastric tube. A chest x-ray was taken, and blood, urine and trachea culture samples were collected. The patient was diagnosed with pneumonia after a pulmonology consultation, and antibiotic therapy was initiated. The patient regained consciousness on the third day after he was admitted. His body temperature dropped to 36.5°C. Five days later serum CK was 868 U/L, AST 59 U/L and ALT 18 U/L. On the fifteenth day of the treatment, antibiotic treatment was switched after observing a WBC value of 15,400 with 88.1% neutrophiles in the patient's blood count. Tracheostomy was performed on the assumption that the treatment process and therefore intubation period would lengthen. The patient had three bronchoscopy procedures performed following another pulmonology consultation after a suspected lesion was seen on the postero-anterior chest x-ray and a rise in body temperature on the first month of treatment. Bronchoscopy culture yielded Acinetobacter baumanii, and blood culture yielded methycilline resistant Staphylococcus aureus. These results were associated with a hospital infection and the patient was isolated, antibiotic therapy was rescheduled based on antibiogram results. Hemofiltration was performed for five days for acute renal failure due to sepsis on the 52nd day after the patient was admitted, when blood urea increased to 147 mg/dl, creatinine value increased to 2.67 mg/dl and urine output ceased. As his general condition worsened progressively and hemodynamics deteriorated, the patient died on the 62nd day after his admission.

Discussion

Malignant syndrome is a rare condition resulting from the discontinuation or dose decrease of drugs used in PD treatment, including levodopa, amantadine and bromocriptine (6,7). Major and minor criteria, previously described for NMS by Levenson, are used for definitive diagnosis. Major criteria are defined as fever, high serum CK, worsening of parkinsonism, and minor criteria are defined as tachycardia, abnormal blood pressure values, tachypnea, loss of consciousness, hyperhydrosis and leucocytosis. A diagnosis of malignant syndrome requires the presence of at least three major or two major and four minor criteria (4).

Discontinuation of drugs by the patient or caretakers because of hallucinations or dyskinesia occurring during levodopa use, physicians' dosage adjustments and discontinuation of drugs or dose decrease during pre-operative period because of deep brain stimulation (DBS) used in PD treatment in recent years, may cause MS (4,6,8). Dehydration, and intervening infections, in particular, accelerate the development of this syndrome (2,6). It is believed that, what triggers the disease process is the sudden discontinuation of the drug, not discontinuation after a long-term use (8). Although it is thought that the minimum period required between discontinuation of levodopa pre-DBS and occurrence of MS is at least 12 hours (9), currently there is no controlled study to determine this period definitively (8). To prevent the development of this conditon, it is recommended to taper off anti-parkinson drugs very gradually (4).

The role of dopamine is of interest in the pathogenesis of malignant syndrome, as in NMS (3,10). Dopaminergic hypofunction in the nigrostriatal system causes worsening in PD symptoms, whereas hypothalamic dopaminergic hypofunction causes autonomic disorders and mesocortical dopaminergic hypofunction causes changes in consciousness (5). Secretion of muscle from the sarcoplasmic reticulum in skeletal muscles increases muscle tone, and secretion of pyrogenic substances in skeletal muscles contributes to increase in body temperature (5). As a result, both central and peripheral pathologies are thought to be involved in the pathogenesis (5,11).

The first step after diagnosing malignant syndrome should be initiating high-dose levodopa treatment via nasogastric tube. If the patient cannot receive oral or enteral nutrition, levodopa should be administered intravenously. Patients should receive fluid replacement of 40-50 ml/kg per day; cold compress application to reduce fever can be very effective. Intravenous dantrolene 80 mg, TID, and bromocriptine 5-10 mg, TID, administered orally or via nasogastric tube should be added to existing therapy (2). One case has been reported to benefit from apomorphine injection added to levodopa treatment (12). Intravenous methylprednisolone 1000 mg/day added to levodopa, bromocriptine, and dantrolene treatment was shown in a study to shorten the disease process and be effective in alleviating symptoms (13).

Electroconvulsive therapy (ECT) can provide benefit in a very short time in cases refractory to drug treatment (14,15). In a case reported from our country, MS symptoms occurred following sudden discontinuation of levodopa, and ECT was administered to the patient who did not respond to drug treatment in four days after neurological examination findings worsened. The patient regained consciousness at the second session and CK level was observed to fall at the end of the fifth session (14). Similarly,

following the ECT treatment Meagher et al. administered to their MS patient resistant to drug treatment for two weeks, the patient's general condition improved at the second session and treatment was completed after eight sessions (15).

As our patient responded to high-dose levodopa treatment in three days in terms of hemodynamic, autonomic functions and laboratory findings, there was no need to administer additional treatment. The cause of death was the later emerging hospital infection resistant to antibiotics, sepsis and acute renal failure.

This case was presented to draw attention to the diagnosis of MS, occurring as a result of sudden discontinuation of PD drugs. One study reported that MS can be seen not only in PD, but also in conditions causing secondary parkinsonism including progressive supranuclear palsy, striatonigral degeneration, multysistem atrophy, vascular parkinsonism, and Lewy body dementia (4). The presence of three cases with only low grade fever and CK increase show that this syndrome can have a benign form (16). On the other hand, in MS resulting from pre-DBS drug discontinuation, DBS is found to alleviate the symptoms, prevent CK increase and therefore delay diagnosis (9).

In conclusion, all patients receiving anti-parkinson drugs and their caretakers should be warned about the possibility of drug discontinuation in cases of anorexia and fatigue due to intervening infections, and informed about MS. Moreover, physicians should be vigilant about the condition and investigate CK values of patients presenting with such a condition.

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