CASE REPORT

Parkinsonism Induced by Sepsis: A Case Report

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ABSTRACT

Background: *Parkinson's disease (PD) is a slowly progressive neurodegenerative disease that appears essentially as a sporadic condition with no identifiable cause. Parkinsonism is used for syndromes where the aetiology is known such as Parkinsonism due to stroke, infection, neuroleptic drugs and toxic agents. Parkinson's disease and Parkinsonism present with the tetrad of tremor at rest, slowness of voluntary movement (bradykinesia), rigidity and a characteristic disturbance of gait and posture. A report of Parkinsonism induced by sepsis is rare. This report aims to create awareness of Parkinsonism as a manifestation of sepsis.*

Method: *The case note of a patient with Parkinsonism induced by sepsis managed in the medical unit of the University of Port Harcourt Teaching Hospital and a review of the literature on the subject with Medline search was used.*

Result: *A 71 year old Nigerian male presented with Parkinsonism on a background of Gram negative sepsis which resolved with antibiotic therapy. Antiparkinoinian drugs were not used.*

Conclusion: *Parkinsonism is a rarely reported neurological complication of sepsis. There is a need for physicians to be aware of this clinical manifestation.*

KEYWORDS: Parkinsonism; Sepsis; Nigerian male.

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INTRODUCTION

Parkinson's disease (PD) is a common slowly progressive neurodegenerative disease that occurs sporadically with no identifiable cause. Clinically, Parkinson's disease is characterized by the tetrad of tremor at rest, slowness of voluntary movements (bradykinesia), rigidity, and a characteristic disturbance of gait and posture[1]. It results mainly from the death of dopaminergic neurons in the substantia nigra pars compacta, frequently accompanied by the presence of ubiquitin-positive eosinophilic intracytoplasmic inclusions, known as Lewy bodies in surviving neurons. Parkinsonism is used for syndromes where the aetiology is known such as Parkinsonism due to stroke, infection, neuroleptic drugs and toxic agents[1].

The prevalence of PD varies in different countries and among different racial group. Generally, Caucasians have a higher prevalence, around 100-350 per 100,000 population. Asians and Black Africans have lower rates, around one-fifth to one- tenth of those in whites[2]. However, age adjusted Parkinson's disease prevalence was not significantly different in whites and blacks in a study done in Mississippi[3]and northern Manhattan, USA[4]. In Nigeria, and prevalence has been put at 67 per 100,000, in a study done in a rural area[5].

The etiology of PD remains mysterious. A number of putative factors are associated with Parkinson's disease, age being the one most consistently agreed upon. Parkinson's disease is less common before 50 years of age and increases steadily with age thereafter up to the ninth decade. Inflammatory response has been widely accepted as a cause of neurodegenerative diseases. Various animal model have been developed to demonstrate dopaminergic system degeneration by intranigral injection of the endotoxin lipopolysaccharide (LPS), a component of gram negative bacteria cell wall and a potent inducer of inflammation[6-8] . Recent observation has confirmed that sepsis is associated with excessive brain inflammation and neuronal apoptosis, which results in various neurological disorders[9]. We report here a case of Parkinsonism induced by sepsis.

CASE REPORT

Mr. I.W. is A 71 year old Nigerian who had been receiving medical care at the out-patient department of the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, after being diagnosed hypertensive five years previously.

During one of his regular out-patient visits, he complained of urinary hesitancy, straining, feeling of incomplete bladder emptying and a decrease force and caliber of urine stream, which had been on for four months. On account of the above symptoms he was referred for urological assessment. Two weeks after the urological referral he complained of a one week history of increased urine frequency, urinary urgency, nocturia over three times per night and suprapubic pain. These symptoms were associated with moderate to high grade intermittent fever; with no chills or rigors.

Three days before presenting to the medical clinic, he noticed he was generally weak, with difficulty in walking, slow movement and tremors at rest in all limbs which

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were worse in the upper limbs; he remained conscious and oriented but seemed occasionally confused. Urological assessment involved a digital rectal examination (DRE) and abdominopelvic ultrasonography which revealed an enlarged prostate. He also had a urethral catheterization in the course of the assessment.

Prior to the onset of these symptoms, he had good blood pressure control, but evidence of hypertensive heart disease (cardiomegaly on chest radiography and Electrocardiography (ECG) revealing atrial fibrillation, biventricular hypertrophy, ventricular ectopics, and right bundle branch block, left anterior fascicular block).

He was not diabetic, did not have a previous history of stroke or transient ischaemic attack (TIA), nor head injury and there was no family history of Parkinsonism. His renal function and lipid profile were within normal limits.

In the course of his out-patient visits, he was on lisinopril, low dose aspirin, prazosin and hydrochlorothiazide, digoxin, folic acid and vitamin B-complex tablets. There was no history of other significant drug use.

On clinical examination, he was conscious and well oriented, febrile (38.4^{o}C), not dehydrated, anicteric and not pale, but had coarse tremors in the upper limbs at rest, there was no asterixis. He had no cranial nerve defects, but had generalized hypertonia with cogwheel rigidity. Normal gross power in all limbs with hypereflexia, but no clonus. Pulse was 92 beats/min, small volume and irregular, Blood pressure was 100/60 mmHg, JVP was not raised, patient had a displaced heaving cardiac apex (6LICS, AAL), with a first and second heart sound only. Abdominal examination revealed suprapubic tenderness and a tender palpable spleen, (4cm below the left subcoastal margin). There were no significant findings on respiratory examination. Fundoscopic examination showed features of Keith Wegner Grade II hypertensive retinopathy.

A provisional diagnosis of sepsis from a urinary Tract Infection (UTI) with Parkinsonism was made. The diagnosis was confirmed by results of complete blood count which revealed leukocytosis = 13.3 x 10^{9}/L, Neutrophillia of 90%, with left shift and toxic granulations. Urinalysis, showed pus cell of 20-22/HPF, 5-7 RBCs/HPF, nil proteinuria, nil glycosuria. Urine culture yielded klebsiella specie and blood culture yielded klebsiella and staphylococcus aureus species. His prostate Specific Antigen (PSA) assay was 2ng/mL within normal limits. No changes were noticed on repeat ECG and there was no evidence of myocardial infarction. His renal and hepatic function tests were normal. Random Blood Sugar assay was 5.6mmol/L.

He was commenced on broad spectrum intravenous antibiotic therapy consisting of ceftriaxone, metronidazole and genticin, which was continued in line with sensitivity reports. Genticin was discontinued on the fifth day, while ceftriaxone and metronidazole where administered for 10 days. He was subsequently converted to oral antibiotics and completed a three week course of antibiotic therapy. Following commencement of treatment clinical features of Parkinsonism and sepsis resolved, with confirmation of resolved sepsis by repeat urine cultures, blood cultures and patient's complete blood count. He has remained well and has been seen continuously in the medical clinic without recurrence of symptoms twelve months after discharge.

DISCUSSION

Sepsis is a systemic inflammatory response to a documented infection. The manifestation of sepsis include temperature greater than 38^{0}C or less than 36^{0}C, tachycardia (> 90 beats/min), tachypnoea (> 20 breath/min) and at least one manifestation of inadequate organ function/ perfusion[10]. Brain dysfunction in sepsis may be related to the action of micro-organism toxins, effect of inflammatory mediators, metabolic alterations and to abnormalities in cerebral circulation[11]. Encephalopathy and polyneuropathy occur in 70% of septic patients[12]. The encephalopathy is usually diffuse and severe and may ensue before signs of other organ failure, but reverses quickly with successful treatment of the sepsis. It has been referred to as "Sepsis Associated Encephalopathy" (SAE) to emphasize the absence of direct infection of the central nervous system[11]. Like other forms of metabolic encephalopathy it presents as confusion, disorientation, agitation and drowsiness or coma[13].

In addition to encephalopathy, patients with sepsis and other critical illnesses can also develop polyneuropathy and myopathy either singly or in combination. Critical illness polyneuropathy (CIP) was first described by Bolton et al. in 1984[14]. It is a sensorimotor polyneuropathy that is often a complication of sepsis and multiorgan failure. Critical illness myopathy (CIM) has been referred to variously as acute quadriplegic myopathy, thick filament myopathy, acute necrotizing myopathy of intensive care and rapidly evolving myopathy with myosin deficiency fibre[15].

Toxic (septic) Parkinsonism has been described in

humans following accidental injection of Salmonella minnesoto lipopolysaccharide in a twenty two year old laboratory worker[16]. Lipopolysacharide (LPS) a component of Gram- negative bacteria cell wall has been shown to cause dopaminergic system degeneration following intranigral injection in mice and rats[6-8]. Loss of catecholamine content, Tyrosine hydroxylase (TH) activity and TH immunostaining has also been demonstrated[7]. This neurotoxic effect in mice and rats has been shown to result from a strong activation of microphage/ microglial cells which are abundant in the substantial nigra. A profuse reactive microglia is seen also in the substantia nigra and striatum, not only in idiopathic Parkinson's disease[17,18] but also in familial Parkinson's disease[19]. Expression of cytokines such as Interleukin- 1 beta, tumour necrosis factor (TNF)-alpha and caspase -11 has also been demonstrated in brain of mice following intranigral injection of lipopolysacharide[20]. Increased level of interleukin-1-beta, interleukin 6 and tumour necrosis factor- alpha have been found in the basal ganglia and cerebrospinal fluid of patients with Parkinson's disease, suggesting a local immune reaction[21].

The patient in the reported case presented with sudden onset Parkinsonism in association with gram negative sepsis from a urinary tract infection which resolved with antibiotic therapy; similarly most cases of sepsis associated encephalopathy are rapidly reversible with the treatment of sepsis as there is no specific treatment for this condition[22]. This pattern of presentation makes sepsis the likely cause of Parkinsonism in the reported case especially with the exclusion of other causes of Parkinsonism.

Case reports have documented patients with acute onset of Parkinsonism following infarction or heamorrhage of the basal ganglia[23-26]. A more insidious progressive form of Vascular Parkinsonism has also been described and is thought to be associated with a more diffuse cortical white matter ischeamia[26,27]. With the patient's advanced age and hypertension(a major vascular risk factor) and evidence of hypertensive heart disease (cardiomegaly on chest radiography and Electrocardiography (ECG) revealing atrial fibrillation, biventricular hypertrophy, ventricular ectopics, right bundle branch block and left anterior fascicular block), the possibility of an embolic phenomenon was borne in mind. However, patient had no history of stroke or transient ischeamic attack (T.I.A) in the past and had no focal neurologic signs on presentation. Unfortunately, a CT scan or MRI was not done as the CT scan was non functional at the time and an MRI was not available. Previous studies have shown that patients with vascular Parkinsonism are more likely to have gait difficulty, dementia, and corticospinal and pseudobulbar findings and less likely to experience tremors[28,29]. A predominantly lower body involvement has also been reported in vascular Parkinsonism[28-31]. The patient in the reported case had tremors which was worse in the upper limb but had no features of dementia, corticospinal and pseudobulbar palsy.

The possibility of a drug induced Parkinsonism was unlikely in this case as there was no history of use of any reserpine containing antihypertensive, phenothiazines or butyrophenones in the last three months preceding the onset of symptoms[32,33]. There was also no history of exposure to carbon disulfide, manganese dust or carbon monoxide poisoning[32].

There were also no features in the patient to suggest other causes of Parkinsonism such as Wilson's disease which would occur in a much younger person in addition to its other features[1,32]. Huntington's disease, Shy-Drager syndrome, cortical basal ganglia degeneration, diffuse Lewy body disease, Creutzfeldt-Jakob disease and Alzheimer's disease are other causes of Parkinsonism which are unlikely in this case due to the acute presentation, the absence of dementia and other neurological features of cortical, subcortical and cerebellar degeneration associated with these conditions[1].

CONCLUSION

Toxic (septic) Parkinsonism is an uncommon clinical condition and is thus rarely reported. Physicians need to be aware of this neurological manifestation of sepsis to enhance appropriate treatment which is the elimination of sepsis and not the use of antiparkinsonian drugs.

REFERENCES

1. Aminoff MJ. Parkinson's disease and other extrapyramidal disorders. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. (Eds) Harrison's Principle of Internal Medicine. 15th Ed. New York: McGraw-Hills. 2001: 2399 2402.
2. Lai BC, Tsui JK. Epidemiology of Parkinson's diseases. British Columbia Medical Journal 2001; 43(3): 133 - 137.
3. Schoenberg BS, Anderson DW, Haerer AF. Prevalence of Parkinson's disease in the Bi-racial population of Copiah County, Mississippi. Neurology1985; 35: 841 - 845.
4. Mayeux R, Marder K, Cote LJ, *et al*. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988-1993. Am J Epidemiol 1995;142:820 - 827.

5. Schoenberg BS, Osuntokun BO, Adeuja AO, *et al*. Comparison of the prevalence of Parkinson's disease in the black population in the rural United States and in rural Nigeria: door to door community studies. Neurology 1988; 38: 645 - 646.
6. Zhou HF, Liu XY, Niu DB, Li FQ, He QH, Wang XM. Triptolide protects dopaminergic neurons from inflammation-mediated damage induced by lipopolysaccharide intranigral injection. Neurobiol Dis 2005;18(3):441-9.
7. Castano A, Herrera AJ, Cano J, Machando A. The degenerative effect of a single intranigral injection of LPS on the dopaminergic system is prevented by dexamethasone, and not mimicked by rh-TNF-alpha, IL-1beta and IFN-gamma. J Neurochem 2002; 81(1):150 - 7.
8. Herrera AJ, Castano A, Venero JL, Cano J, Machando A. The single intranigral injection of LPS as a new model for studying the selective effects of inflammatory reactions on dopaminergic system. Neurobiol Dis 2000;7(4):429 - 47.
9. Sharshar T, Hopkinson NS, Orlikowski D, Annane D. Science review: The brain in sepsis- culprit and victim. Critical Care 2005; 9(1): 37 - 44.
10. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101(6):1644 - 55.
11. Consales G, De Gaudio AR. Sepsis associated encephalopathy. Minerva Anestesiol 2005; 71(1-2):39 - 52.
12. Bolton C F, Young GB, Zochodne DW. The neurological complications of sepsis. Ann Neurol 1993; 33(1): 94 - 100.
13. Senap MN, Worthley LI. Neurologic complications of critical illness: part I. Altered States of consciousness and metabolic encephalopathies. Crit Care Resusc 2002;4(2): 119 - 32.
14. BoltonCF, GilbertJJ, Hah AF, Sibbald WJ. Polneuropathy in critically ill patients. J Neurol Neurosurg Psychiat1984;47:1223 - 31.
15. Motomura M. Critical illness polyneuropathy and myopathy. Rinsho Shinkeigaku. 2003; 43(11):802 - 4.
16. Ines N. Parkinsonism caused by lipopolysaccharides in the CNS(a case report). International Congress on Parkinson's Disease. 2001. Helsinki, Finland.
17. Yamada T, McGeer PL, McGeer EG. Relationship of complement-activated oligodendrocytes to reactive microglia and neuronal pathology in neurodegenerative disease. Dementia 1991; 2:71 - 77.
18. McGeer PL, Itagaki S, Boyes BE, et al. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology 1988; 38:1285-1291.
19. Yamada T, McGeer EG, Wszolek ZK, *et al*. Histological and biochemical pathology in a family with autosomal dominant parkinsonism and dementia. Neurol Psychiatry Brain Res 1993; 2:26-35.
20. Arai H, Furuya T, Yasuda T, Miura M, Mizuna Y, Mochizuki H. Neurotoxic effects of lipopolysaccharide on nigral dopaminergic neurons are mediated by microglial activation, interleukin-1beta, and expression of caspase-11 in mice. J Biol Chem 2004; 279(49):51467 53.
21. McGeer PL, Yasojima K, McGeer EG. Inflammation in Parkinson's disease. In: Calne D, Calne S (Eds). Parkinson's Disease. Advances in Neurology. Philadelphia:Lippincott Williams & Wilkins. 2003.
22. Leon A, Lepouse C, Floch T, Graftieaux JP. Brain injury during severe sepsis. Ann Fr Anesth Reanim 2006; May 9[Epublication ahead of print] available online 11 may 2006. At www.doi:10:1016:/j.annfar.2006.03.011.
23. Tolosa ES, Santamaria J. Parkinsonism and basal ganglia infarcts. Neurology1984; 34: 1516-1518.
24. Friedman A, Kang UJ, Tantemichi TK, Burke RE. A case of Parkinsonism following striatal lacunar infarction. J Neurol Neurosurg Psychiatry 1986; 49: 1087-1088.
25. Relder-Groswasser I, Bornstein NM, Korczyn AD. Parkinsonism in patients with lacunar infarcts of the basal ganglia. Eur Neurol 1995; 35: 46 - 49.
26. Zijlmans JCM, Thijssen HOM, Volgels OJM, et al. MRI in patients suspected of vascular Parkinsonism. Neurology 1995; 45: 2183 - 2188.
27. Chang CM, Yu YL, Ng HK, et al. Vascular pseudoparkinsonism. Acta Neurol Scand 1992; 86: 588 - 592.
28. Winikates J, Jankovic J. Clinical correlates of vascular Parkinsonism. Arch. Neurology 1999;56: 98 -102.
29. Critchley M. Arteriosclerotic Parkinsonism. Brain 1929; 52: 23 - 83.
30. FitzGerald PM, Jankovic J. Lower body Parkinsonism; evidence for a vascular etiology. Mov Disord 1989; 4: 249 - 260.
31. Zijlmans JCM, Poels PJE, Duysens J, et al. Quantitative analysis in patients with vascular Parkinsonis. Mov Disord 1996; 11: 501 - 508.
32. Quinn N. Parkinsonism: recognition and differential diagnosis.BMJ 1995; 310:447 - 52.
33. Stephen PJ, Williamson J. Drug-induced Parkinsonism in the elderly. Lancet 1984; II: 1082-1083.