PAPER

J R Coll Physicians Edinb 2007; **37**:202–204

Hypomagnesaemia induced Parkinsonism?

[1]MPW Chua, [2]KM McLaughlin, [3]SB Rochow
[1]Specialist Registrar, [2]Senior House Officer, [3]Consultant, Department of Medicine for the Elderly, Woodend Hospital, Aberdeen, Scotland

ABSTRACT We report an unusual presentation in an elderly woman with a previous diagnosis of benign tremulous Parkinson's disease who developed a severe Parkinsonian-like syndrome with profound immobility following small bowel resection. Her Parkinsonism was largely unresponsive to conventional medical therapy. However, she was found to be profoundly hypomagnesaemic and a dramatic improvement in her symptoms and functional ability was achieved after correction of the severe hypomagnesaemia. A brief discussion is included.

KEYWORDS Hypomagnesaemia, Parkinson's disease, short bowel syndrome

LIST OF ABBREVIATIONS 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 1-methyl-4-phenylpyridinium(MPP), Department Of Medicine for the Elderly (DOME), N-Methyl-D-Aspartate (NMDA), short bowel syndrome (SBS)

DECLARATION OF INTERESTS No conflict of interests declared.

Published online ***July 2007***

Correspondence to ***Department of Medicine for the Elderly, Woodend Hospital, Eday Road, Aberdeen, AB15 6XS***

tel. ***+44 (0)1224 556 390***

fax. ***+44 (0)1224 556 339***

e-mail ***stuart.rochow@nhs.net***

INTRODUCTION

In recent times, magnesium has been a largely overlooked intracellular cation, despite being involved in a large number of cellular metabolic reactions. In current clinical practice, serum magnesium levels are not normally routinely requested as part of the clinical assessment.

However, it has been found that the estimated prevalence of hypomagnesaemia in the general population ranges between 2·5–15% with inter-racial variability.[1] There is also a reported increase of magnesium requirements amongst the elderly as a result of poor intake, poor intestinal absorption and increased renal clearance.[2] Patients with hypomagnesaemia can present with cardiac dysrhythmias, neurological manifestations (e.g. seizures, tremors, generalised weakness, myoclonic jerks and ophthalmoplegia) and central nervous system disturbances.

However, there are no case reports to our knowledge involving hypomagnesaemia and Parkinson's Disease. Although this link has been speculated for some time, there are only patients' testimonial reports of Parkinsonism improving with magnesium supplements.[3]

CASE REPORT

A 79-year-old woman with a previous history of hemicolectomy for Dukes' B carcinoma was admitted to general surgery with small bowel obstruction. Four years earlier, she had been diagnosed with benign tremulous Parkinson's Disease by a consultant neurologist and was commenced on co-beneldopa with limited clinical response. A subsequent 123I FP-CIT Loflupane DaTSCAN© demonstrated lack of uptake (of isotope) in both putamen consistent with a Parkinsonian syndrome.

In theatre, emergency small bowel resection was performed and two separate small bowel tumours were located. An ileostomy was successfully fashioned but she failed to mobilise post-operatively despite being previously independent. The patient was therefore referred to a consultant geriatrician with a special interest in Parkinson's Disease and was transferred to DOME for assessment and rehabilitation. The main concerns upon transfer to DOME were weight loss, excessive ileostomy output and marked deterioration of her Parkinsonian symptoms. The latter was characterised by severe bilateral upper limb rest tremor, marked upper and lower limb rigidity and bradykinesia. She was bedbound requiring full nursing care. The co-beneldopa dose was gradually increased to 700 mg daily with subsequent addition of Ropinirole to a total daily dose of 9 mg with no significant response over a two-week period.

Subsequent blood tests revealed hypocalcaemia of 1·53 mmol/L (corrected) (normal 2·2–2·6 mmol/L) which improved to 1·90 mmol/L after commencement of oral calcium supplements without clinical improvement. Further blood tests revealed profound hypomagnesaemia of <0·05 mmol/L (normal 0·70–0·90 mmol/L) which was immediately corrected with intravenous magnesium and serum calcium levels correspondingly returned to normal. Within three days of normalisation of her serum magnesium levels, the patient was able to mobilise short distances with the help of a walking (Zimmer) frame. However, her mobility and functional ability fluctuated with her serum

magnesium levels. Advice was sought from gastroenterology colleagues with regard to decreasing ileostomy output and serum magnesium levels were eventually stabilised using a combination of anti-motility agents and oral magnesium salts.

Within four weeks, the patient was transformed from being bedbound and requiring full nursing care, to being able to self-care and was discharged to temporary sheltered housing. At the point of discharge, bradykinesia and rigidity had largely resolved and the tremors had markedly improved. At subsequent monthly outpatient reviews, ropinirole and co-beneldopa were gradually withdrawn, without any deterioration of Parkinsonian features, and serum magnesium levels were correspondingly maintained.

DISCUSSION

In our patient, severe hypomagnesaemia as a consequence of decreased gastrointestinal absorption secondary to short bowel syndrome, seemed to have exacerbated a Parkinsonian-like syndrome in a patient who previously suffered from only mild rest tremor. The Parkinsonian features responded dramatically to magnesium replacement and we are not aware of any similar published case. There are several anecdotal testimonials of magnesium supplements published on commercial health supplement websites[3] which have suggested the improvement of Parkinsonian symptoms but there are no reports of hypomagnesaemia exacerbating Parkinsonism.

The main pathological feature of Parkinson's disease is gradual loss of dopaminergic neurons in the *substantia nigra pars compacta* resulting in a loss of dopaminergic input to the basal ganglia via the nigrostriatal pathway. This results in an imbalance in the output pathways of the striatum forming the extrapyramidal system resulting in motor symptoms typical of this disorder. An overactivity of the glutamatergic subthalamic nucleus following dopaminergic denervation leading to an increase of striatal glutamate release is one of the biochemical changes observed.[4] Studies have shown that pharmacological inhibition of the glutamatergic system with a NMDA antagonist can improve parkinsonism.[5]

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine is manufactured accidentally in the illegal production of opiod analgesic drug. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine is metabolised into MPP, a neurotoxin which selectively destroys dopaminergic neurons and causes anatomical, biochemical and behavioural manifestations similar to Parkinson's Disease.[5] A study on MPTP-lesioned parkinsonian monkeys[6] concluded that magnesium sulphate, a NMDA antagonist[7] as monotherapy, did not have any significant anti-Parkinsonian effects but did improve levodopa-induced dyskinesias.[8]

Magnesium is known to be involved in a large number of cellular metabolic reactions and its deficiency usually manifests itself early, leading to a multitude of neurological symptoms such as limb weakness, tetany and even ataxia. In patients with hypomagnesaemia, the calcium release from the sarcoplasmic reticulum is increased, and as magnesium is required for calcium re-uptake, muscles tend to be more susceptible to contractions to a given stimulus, but are less able to recover from the contraction leading to signs of tetany.

In our patient, the marked upper and lower limb rigidity was most likely the result of her profound hypomagnesaemia and concomitant hypocalcaemia which exacerbated her Parkinsonian symptoms. Her profound disability improved dramatically with the replacement of her serum magnesium levels parenterally. This causal link was further established by the subjective assessment of functional fluctuations our patient had as a result of difficulty maintaining her serum magnesium levels.

However, there was an oversight in the management of our patient's hypomagnesaemia. It is well-established that serum magnesium levels are an unreliable measure of total body magnesium levels.[9] The general consensus for measuring magnesium deficiency is the magnesium loading test which is both a therapeutic and diagnostic procedure. Unfortunately, we did not carry out this test confirming her total body magnesium levels, but felt that with consecutive laboratory analysis of undetectable and low levels of serum magnesium, we were convinced that the patient was markedly hypomagnesaemic.

Short bowel syndrome is a result of extensive loss of the small bowel leading to a malabsorptive state.[11,12] The main treatment aims are maintaining hydration, nutrition and correcting electrolyte imbalances. However, these cannot normally be achieved unless stoma output is controlled.[13] Gastrointestinal absorption of magnesium occurs in the small bowel particularly the ileum[14] and colon,[15] extensive parts of which were previously resected in our patient. Therefore, due to her high stomal output, patient subsequently suffered from metabolic disturbances of hypocalcaemia and hypomagnesaemia.

Upon initial contact with our patient, we had suspected poor absorption of medications as the primary cause of the patient's worsening Parkinsonism. However, the absorption of levodopa is largely carried out in the proximal small intestine[16] which was mostly intact in our patient. Furthermore, no visible tablet remnants were found on examination of the stoma bag. Additionally, the bioavailability of levodopa is independent of magnesium levels.[17]

We had initially considered hypocalcaemia as the cause of the increased muscle rigidity, but the absence of typical features of tetany, and with no corresponding functional improvement with calcium supplementation albeit serum

calcium levels, were still below the normal range. The dramatic response to magnesium replacement leads us to conclude that the patient developed a metabolic myopathy principally secondary to hypomagnesaemia. This, superimposed on a patient with pre-existing Parkinsonian tremor gave the appearance of someone with much more advanced disease.

CONCLUSION

This case highlights some of the challenges of managing elderly patients with multiple co-morbidities. It also emphasises the importance of closer collaboration between surgeons, physicians and nurse specialists in the management of pre- and post-operative Parkinson's disease patients.[18] In hindsight, we should have anticipated the potential problems of managing a patient with short bowel syndrome and sought specialist advice at an earlier stage. However, Parkinson's disease patients are still currently facing potential interruptions to their medication regime during the pre- and post-operative periods which may precipitate their exacerbations.

REFERENCES

1 Ma J, Folsom AR, Melnick SL *et al.* Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study. *J Clin Epidemiol* 1995; **48:**927–40.

2 Seelig MS, Preuss HG. Magnesium metabolism and perturbations in the elderly. *Geriatr Nephrol Urol* 1994; **4:**101–11.

3 www.hippocrates.com.au/magnesium.html

4 Calabresi P, Mercuri NB, Sancesario G, Bernardi G. Electrophysiology of dopamine-denervated striatal neurons. Implications for Parkinson's Disease. *Brain* 1993; **116:**433–52.

5 Dean AL, Stuart AL. Potential and current use of N-Methyl-D-Aspartate (NMDA) receptor antagonists in diseases of aging. *Drugs & Aging* 2001; **18(10):**717–24.

6 Burns RS, Chiueh CC, Markey SP, Ebert MH, Jacobowitz DM, Kopin IJ. A primate model of Parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Proc Natl Acad Sci USA* 1983; **80(14):**4546–50.

7 DeCollogne S, Tomas A, Lecerf C, Adamowicz E, Seman M. NMDA receptor complex blockade by oral administration of magnesium:comparison with MK-801. *Pharmacol Biochem Behav* 1997; **58(1):**261–8.

8 Chassain C, Eschalier A, Durif F. Antidyskinetic effect of magnesium sulfate in MPTP-lesioned monkeys. *Exp Neurol* 2003; **182:**490–6.

9 Potter JD, Robertson SP, Johnson JD. Magnesium and the regulation of muscle contraction. *Fed Proc* 1981; **40(12):**2653–6.

10 Reinhart RA. Magnesium metabolism. A review with special reference to the relationship between intracellular content and serum levels. *Arch Intern Med* 1998; **148:**2415–20.

11 Bannerjee A, Warwicker P. Acute renal failure and metabolic disturbances in the short bowel syndrome. *Q J Med* 2002; **95:**37–40.

12 Tong GM, Rude RK. Magnesium deficiency in critical illness. *J Int Care Med* 2005; **20(1):**3–17.

13 Nightingale JM. Management of patients with a short bowel. *World J Gastroenterol* 2001; **7(6):**741–51.

14 Kayne LH, Lee DB. Intestinal magnesium absorption. *Miner Electrolyte Metab* 1993; **19(4–5):**210–17.

15 Hardwick LL, Jones MR, Brautbar N, Lee DB. Site and mechanism of intestinal magnesium absorption. *Miner Electrolyte Metab* 1990; **16(2–3):**174–80.

16 Nyhom D. Pharmacokinetic optimisation in the treatment of Parkinson's disease: an update. *Clin Pharmacokinet* 2006; **45(2):**109–36.

17 Nomoto M, Nakatsuka A, Nagai M *et al.* Inter- and Intra-individual pharmacokinetic variations in the treatment of Parkinson's Disease. *Rinsho Shinkeigaku* 2005; **45(11):**895–8.

18 Barber M, Stewart D, Grosset D, MacPhee G. Patient and carer perception of the management of Parkinson's disease after surgery. *Age Ageing* 2001; **30:**171–2.