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CASE SERIES

Late Fluctuations in Idiopathic Parkinson's Disease: Treatment with GM1

Domínguez Raúl Omar[1]*, Vila José Francisco[2], Bianchi Graciela Ada[1], Serra Jorge Alberto[1] and Marschoff Enrique[1]

[1]*Hospital Sirio Libanés, Universidad de Buenos Aires, Buenos Aires, Argentina*

[2]*Clínica Sagrada Familia, Universidad de Buenos Aires, Buenos Aires, Argentina*

***Corresponding author:** *Domínguez Raúl Omar, Hospital Sirio Libanés, Universidad de Buenos Aires, Buenos Aires, Argentina*

Abstract

The diagnosis and severity of Parkinson's disease are established by clinical criteria. The motor manifestations predominate while few are sensory. Initially, treatment includes dopaminergic drugs and/or agonists with good results in the first years. Later symptoms appear requiring different therapeutic strategies. Here, we present the results of a series of patients with late fluctuations treated with monosialo-ganglioside. Seven patients older than 70 years, treated for idiopathic Parkinson's, presented combined motor and sensory fluctuations: four painful foot dystonias, one painful freezing, and two camptocormia with low back pain. After the increase in levodopa and the addition of agonists without favorable results, gangliosides were applied intramuscularly on alternate days, maintaining a fixed dose of levodopa and agonists, for 3 months. The Initial and final values of pain, determined with the Visual Analogic Scale and motor fluctuations with the unified Parkinson disease rating scale and compared with the one-tailed Wilcoxon assuming the null hypothesis that the treatment was not successful. In the second week of evaluation, improvements were observed in the seven patients. The probability of seven sucesses in seven trials under the null hypothesis is 0.0078l thus it was rejected. Dopaminergic drugs, useful in the first years of treatment have uncertain effects on the motor and sensory fluctuations appearing later. The use of gangliosides at this stage was useful, improving these late manifestations, including camptocormia.

Keywords

Idiopathic Parkinson's, Late fluctuations, Dystonias, Freezing, Camptocormia, GM1

Abbreviations

IPD: Idiopathic Parkinson's Disease; GM1: Monosialo-Tetrahexosyl-Gangliosides; MF: Motor Fluctuations; PF: Pain Fluctuations; H-Y: Hoehn and Yahr stages; VAS: Visual Analogue Scale; MDS-UPDRS: Movements Disorders Society-Unified Parkinson Disease Rating Scale; CptC: Camptocormia

Introduction

Idiopathic Parkinson's disease (IPD) is a neurodegenerative disorder with decreased production of brain dopamine. Clinical manifestations include bradykinesia, rest tremor, hypertonia, cogwheel rigidity, short step length and elevation, altered postural reflexes. There are diagnostic criteria to consider IPD as probable [1]. Years after starting a first therapy, some patients present involuntary movements, such as dyskinesias and dystonia, which make it necessary to program new drugs and doses. Sometimes these fluctuations are associated with pain, and muscle analgesic drugs have uncertain results. Pain in IPD, influences quality of life and its prevalence is approximately 40% [2]. In controlled trials in IPD with pain, monosialo-tetrahexosyl-gangliosides (GM1), developed from porcine brain, were superior to placebo in controlling symptoms without undesirable effects [3]. Thirty years ago, anti-GM1 antibodies and intramuscularly use of GM1, with the pathogenesis unknown, were erroneously attributed to causing acute polyradiculoneuritis [4]. At

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present, anti-GM1 antibodies, without having received treatment with GM1 parenteral, patients develop Guillain Barre syndrome and the presence of antibodies are considered as diagnostic criteria for this last disease [5]. Likewise, the experimental increase in GM1 levels is protective in IPD models induced by α-synuclein [6,7]. By these references obtained, we were induced to use intramuscularly GM1 in late complications of IPD. The objective of this study, carried out prospectively and longitudinally, consisted in the analysis of the evolution of motor fluctuations with pain in seven patients, from a baseline pre-treatment stage until the end of three months of GM1, with biweekly controls.

Methods

Between January and November 2022, we selected 7 patients with IPD from the outpatients of two general hospitals who presented late motor fluctuations (MF) and pain fluctuations (PF), meeting the diagnostic criteria for IPD [1], Table 1 describes their demographic date. Before the start of the study, the patients accepted and signed an informed consent approved by the Hospital Ethics Committee in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards, to receive a 100 mg ampoule of GM1 intramuscularly every other day for 3 months, controlled biweekly with the purpose of evaluating MF and PF. GM1 is a drug authorized by the Ministry of National Health of Argentine, certificate N° 39.097, for free sale, indicated as neurotrophic and neuroprotective. The severity of IPD was assessed according to the Hoehn and Yahr stages (H-Y) [8]. All had a Folstein Minimum Mental State [9] ≥ 26, without any psychotic manifestations. Pain intensity was categorized by the Visual Analogue Scale (VAS) [10]. IPD fluctuations were assessed with the Movements Disorders Society - Unified Parkinson Disease Rating Scale (MDS-UPDRS) [11]. Statistical analysis of the results was conducted applying the one-tailed Wilcoxon test [12] to the differences between the initial value and after 3 months in the measured variables. We assume the null hypothesis that GM1 has no effect against MF or PF.

Results

The symptoms, the initial medication and the late fluctuations were different in each patient. The results of the evaluations are found in Table 2. The patients

Table 1: Demographic date and late fluctuations in idiopathic Parkinson's disease.

Case- Sex	Age in years	Years of IPD	Hoehn y Yahr	Freeze gait	Dystonia feet -off-	CptC
1-M	78	11	3		M	
2-M	81	10	3	M		
3-M	74	11	4		M	
4-F	79	7	3		S	
5-M	76	9	4			M
6-F	74	7	4			S
7-M	72	9	3		S	

Footnotes: Demographic characteristics of the patients, sex, age, years of IPD, its severity, and motor fluctuations that can be mild (L), moderate (M), or severe (S), along the lines base or pre-treatment.

Table 2: Assessment of late fluctuations in IPD.

Case	Hoehn Yahr	Freeze gait	Dystonía of feet -off-	Posture CptC	UPDRS MOTOR	VAS	D/W
1-PRE/ POST	3 2		Yes-M Yes-L		37/ 24	6/ 3	6/ 2
2- PRE/ POST	3 2	Yes-M Yes-L			40/ 26	5/ 2	7/ 1
3- PRE/ POST	4 3		Yes-M Yes-L		52/ 38	6/ 2	5/ 1
4- PRE/ POST	3 2		Yes-M Yes-L		33/ 23	7/ 3	6/ 3
5- PRE/ POST	4 2			yes-M Yes-L	49/ 24	5/ 1	7/ 4
6- PRE/ POST	4 2			Yes-M Yes-L	55/ 28	8/ 3	7/ 3
7- PRE/ POST	3 2		Yes-S Yes-L		35/ 21	9/ 2	6/ 1

Footnotes: Shows pre-treatment (PRE/) and post-treatment (POST) characteristics with GM1, IPD severity (Hoehn-Yahr), motor fluctuations (UPDRS3) and associated pain that may be mild (L), moderate (M) or severe (S), according to the visual analog scale of pain (VAS). Days of the week (D/W) of appearance of the fluctuations.

underwent 1.5 Tesla magnetic resonance imaging of the brain and had no specific abnormalities, in 2 of them the thoracic lumbar spine (numbers 5 and 6), showed disc degeneration without a narrow canal and paravertebral muscles without atrophy or lipid infiltration. All patients underwent kinesiology for IPD and the manifestations that appeared. **Patient 1**, with rest tremor in the left hand and bradykinesia. He started levodopa/carbidopa 125 mg. every 6 hours and at 5 years she doubled the dose. At 8 years, when she woke up, she noted painful internal torsion dystonia of the feet, at rest and when walking. **Patient 2**, bradykinesia and anteropulsion. He started levodopa/benserazide 125 mg every 6 hours, improving for 6 years. Symptoms reappeared, adding pramipexole 1 mg. every 12 hours recovering another 3 years. Then it appeared unpredictable freezing and muscle aches. **Patient 3**, slowness in tasks with generalized hypertonia. He started ropirinol 1 mg. every 12 hours relieving the symptomps for 4 years. When resting tremor in the hands appeared ropirinol was doubled and started taking levodopa/carbidopa 125 mg. every 6 hours, up to 11 years of IPD. There she presented painful torsion dystonia in both feet. **Patient 4**, rest tremor in the right hand. She was medicated with piribedil 50 mg every 12 hours. She was tremor free for 6 years. She presented bradykinesia, and short, shuffling steps. She adds levodopa/benserazide 125 mg. every 6 hours improving for 3 years. Then painful dystonic FM appeared in feet. **Patient 5**, resting tremor in both hands and anteroflexion, medicated with piribedil 50 mg/day and levodopa/carbidopa 125 mg every 6 hours, showing improvements for 5 years. Low back pain and anterior dorsiflexion of 30 degrees appeared; lying down normalized the spinal axis. In 2 years the flexion increased to 45 degrees. Diagnosis: painful camptocormia (CptC) concomitant with IPD. **Patient 6**, bradykinesia and tremor at rest in the hands. She started on levodopa/carbidopa 125 mg. every 6 hours, improving for 6 years. When short and shuffling steps a tendency to freezing when turning and antero-flexion appeared, she started ropirinole 2 mg/day. The posture in 50-60 degree dorsal-lumbar flexion was presented two years later. Diagnosis: Painful CptC in previous IPD. **Patient 7**, walking slowly with shuffling steps, hypertonia in the 4 limbs. He was started on levodopa/carbidopa 125 mg every 6 hours and motor skills improved. Rest tremor appeared in both hands 6 years later. He added piribedil 50 mg every 12 hours, improving. 3 years later FM and FS in feet. The Wilcoxon (one tailed) test was applied to the differences between the values initial and at 3 months. Under the null hypothesis of no effect of the treatment the difference between the initial and final values follow a binomial distribution with N = 7, p = q = 0.5. Obtaining 7 successes out of 7 trials has a probability of 0.0078. Thus we reject the null hypothesis, accepting that the treatment has a positive effect on the late fluctuations in IPD.

Discussion

After 4 or 6 years of IPD treatment, it becomes necessary to vary the initial therapy, dividing it in shorter intervals and adding agonists. Four patients presented dystonia, persistent muscle contraction, accompanied by involuntary postures. These dystonias, usually accompany IPD after several years of treatment. Painful end-of-dose dystonia, usually were located in the feet, preventing walking, affecting the quality of life. Analgesic drugs usually are not effective in painful dystonia, neither baclofen, benzodiazepines, cyclobenzaprine, lithium, and other muscle relaxants. Injection of botulinum toxin showed good relaxing effect [13]. An anticipatory strategy for MF and PF in IPD is to postpone the prescription of levodopa or to prescribe small, divided daily doses. In surgery, deep brain stimulation of the subthalamic nucleus has achieved reduction of end-of-dose dystonia. In this series of cases with painful foot dystonia in IPD, there was a good response to GM1 intramuscular, allowing control of motor and sensory symptoms. Freezing is a phenomenon where patients treated with levodopa go from good mobility to immobility, Worsening might be slow and progressive and, as the patient perceives it, realizing that it is going to occu is considered a predictable motor disorder. Freezing might also occur abruptly at the end or in the middle of the levodopa ingestion, being sudden, abrupt and unpredictable. Impredictable freezing might accompanied by widespread muscle soreness. This unpredictable form occurred in case 2. The pain and hypertonia, with inappropriate postures, are caused by an abnormality of the central nervous system. In this case, GM1 was useful, equivalent to boosting levodopa. Studies analyzed the effect of GM1 on IPD and their most appropriate conclusion was dopamine neurotransmission [14]. CptC consists of a slow and progressive thoracic and lumbar flexion, whose severe state presents the trunk parallel to the floor (anthropoid posture), 45 degrees of flexion is considered the initial stage of CptC. Patients with IPD and CptC have pain in the thoracic and lumbar spine. The development of CptC is associated with several diseases (multisystem atrophy, Lewy body dementia, Alzheimer's, generalized dystonia, amyotrophic lateral sclerosis, myopathy and myositis, myasthenia, hypothyroidism, narrow lumbar canal) and medications (Divalproate, Olanzapine, Pramipexole, Ropirinole). In epidemiological studies IPD and CptC coexist in 3 to 17% and the IPD develops 6 to 8 years before. We found no reports of GM1 administered in CptC. Other therapeutic approaches include physical therapy, corrective orthoses, and deep brain stimulation [15]. We conclude that although this trial was performed in a small number of patients, the response obtained justifies considering the GM1 applied intramuscularly to alleviate the symptoms of MF and PF in advanced IPD, including CptC. These findings need to be confirmed in a larger number of patients and with prolonged follow-

up, since there are few benefits with the drugs in regular use. If fluctuations appear years later with first-line oral of treatments, second-line therapeutic strategies should be applied among them GM1.

Conflict of Interest

The authors declare that they have no conflict of interest. The authors have no financial or proprietary interests in any material discussed in this article.

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