The arrival of levodopa in Catalonia: the experience of Enric Gabàs i Vilella

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ABSTRACT

Introduction and objective. Levodopa is one of the most remarkable advances of neuropharmacology. Its use became widespread following the extraordinary results reported in 1969 by George C. Cotzias in North America. The purpose of this article is to describe the arrival of levodopa in Catalonia.

Methods. We searched for and reviewed the available evidence on the early use of levodopa in Catalonia and the rest of Spain.

Results. In Barcelona, Agustín Codina Puiggròs published a review of the work of Cotzias and other researchers in the first issue of *Medicina Clínica* of 1970, concluding that, should the optimistic results be confirmed, levodopa would emerge as an "effective therapeutic weapon to fight Parkinson's disease, particularly with regard to akinesia," proving to be superior to the medications and stereotactic surgical procedures available at the time. The first study into levodopa in Catalonia and the rest of the Iberian Peninsula was conducted by Dr Enrique Gabàs Vilella under the direction of Dr Adolfo Ley Gracia, and began in April 1969. Ley and Gabàs reported their experience at the Spanish Society of Neurology's Annual Meeting in Barcelona on 12 December 1969, and published their findings in the 54th volume of *Medicina Clínica*, in 1970. After this preliminary study of 6 patients, Gabàs contributed an additional 44 cases treated with levodopa over the following 4 years, and defended his doctoral thesis in 1973, confirming the results published by Cotzias. The use of levodopa became widespread in Barcelona and Catalonia, Madrid, and Bilbao.

Conclusions. In Catalonia, always open to the world's novelties and advances, levodopa arrived as early as April 1969, with Enrique Gabàs.

KEYWORDS

Levodopa, Parkinson's disease, Enric Gabàs i Vilella

Introduction

Levodopa (L-DOPA) is one of the most remarkable advances in the history of neuropharmacology. Used for the treatment of Parkinson's disease for over 50 years, it continues to be the symptomatic treatment of choice for the disease.[1-3]

Dihydroxyphenylalanine was first synthesised in 1911 by Casimir Funk. In 1913, Markus Guggenheim of Hoffmann-La Roche isolated levodopa from broad bean seeds (*Vicia faba*), chemically characterised the compound, and developed a simplified method for its synthesis.[4] Several decades later, in the 1950s, pioneering studies by the Nobel laureate Arvid Carlsson and colleagues enabled the characterisation of dihydroxyphenylalanine as a reserpine antagonist[5]; the group concluded that the neurotransmitter dopamine played a key role in motor control.[6] These advances led

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to the introduction of L-3,4-dihydroxyphenylalanine (levodopa), a dopamine precursor that can cross the blood-brain barrier, with numerous patients being successfully treated in the 1960s. It was initially used for the treatment of reserpine-induced akinesia,[7] and subsequently for the treatment of akinesia in the context of Parkinson's disease, and delivered via the intravenous[8,9] and oral routes.[10,11] In 1961, an Austrian research group, led by Walther Birkmayer and Oleh Hornykiewicz in Vienna, and a Canadian research group, led by André Barbeau in Montreal, independently demonstrated that intravenous and oral levodopa, respectively, significantly improved symptoms, although its effects were short-lived. Several neurologists used low-dose intravenous levodopa and even higher doses of oral levodopa, but failed to achieve satisfactory results.[12] In 1967, George C. Cotzias, a pharmacologist at Brookhaven National Laboratory, in Upton (New York), used higher doses of D,L-DOPA (up to 16 g/day), reporting spectacular results.[13] Subsequently, Curt Porter of Merck & Co. demonstrated that levodopa was the active stereoisomer, reducing the effective dose by half.[14]

In 1969, levodopa was established as an effective and clinically applicable treatment for motor alterations in Parkinson's disease. Cotzias administered increasing doses of levodopa (up to 8 g/day) over long periods of time, demonstrating that the drug achieved significant, long-lasting improvements in Parkinson's disease symptoms.[15] Subsequent multicentre studies,[16] including an extensive study conducted in North America[17] and promoted by Hoffmann-La Roche, confirmed the efficacy and safety of levodopa and supported its approval in the United States in 1970. The main secondary effects of high-dose levodopa, such as dyskinesia and motor fluctuations, also became apparent at that time.[18] It was discovered in the early 1970s that the addition of a peripheral DOPA-decarboxylase inhibitor to levodopa reduced the adverse reactions and improved symptom control. Alfred Pletscher and his colleagues at Hoffmann-La Roche[19] synthesised benserazide (Ro 4-4602), a DOPA-decarboxylase inhibitor that, combined with levodopa, enabled lower doses of the latter drug while reducing adverse reactions.[20] The combination of L-DOPA and benserazide was marketed under the brand name Madopar.® In 1971, Victor Lotti[21] demonstrated that the use of carbidopa (DL-α-methyl-α-hydrazino-3,4-dihydrophenylpropionic acid [HMD]), another DOPA-decarboxylase inhibitor synthesised and patented by Merck, further decreased the therapeutic dose of L-DOPA. The combination of L-carbidopa and L-DOPA was marketed in 1972 under the brand name Sinemet®, and was approved by the United States Food and Drug Administration on 2 May 1975.

Levodopa soon arrived in Catalonia, always open to world's novelties and advances.

Methods

We searched for and reviewed the available evidence on the use of levodopa in Catalonia and the rest of Spain.

Results

In Barcelona, Agustín Codina Puiggròs[22] published the editorial "Bioquímica de la enfermedad de Parkinson" (biochemistry of Parkinson's disease) in the first issue of *Medicina Clínica* of 1970; the article reviewed several studies, including those by Carlsson,[23] Hornykiewicz,[8,24] Barbeau,[25] and Cotzias,[13] and focused on the aetiopathogenesis of the disease. In the section on new therapies in the same issue of the journal, Codina Puiggròs[26] published another study entitled "Tratamiento de la enfermedad de Parkinson con la L-DOPA" (treatment of Parkinson's disease with L-DOPA), asserting that the available evidence confirmed that Parkinson's disease and post-encephalitic parkinsonism are associated with decreased dopamine concentration in the striate body and locus niger, and decreased urinary excretion of dopamine, and suggested that increasing dopamine levels may improve parkinsonian syndromes. He notes that dopamine cannot cross the blood-brain barrier, explaining the development of dihydroxyphenylalanine, a dopamine precursor. Codina also mentions the results reported by Cotzias et al.[13,15] in 1967 with D,L-DOPA, and in 1969 with L-DOPA, in 28 patients with essential or idiopathic Parkinson's disease, post-encephalitic parkinsonism, and probable atherosclerotic or vascular parkinsonism, according to the diagnostic criteria of the time.[27] All patients achieved clinical improvements, especially in akinesia, but also in rigidity, tremor, voice modulation, salivation, sialorrhoea, and writing. Improvements were described as dramatic in ten patients, due to their excellent response, noteworthy in ten, and moderate in four, whereas the remaining four patients only displayed improvements in their general and mental health. Adverse drug reactions included nausea, vomiting,

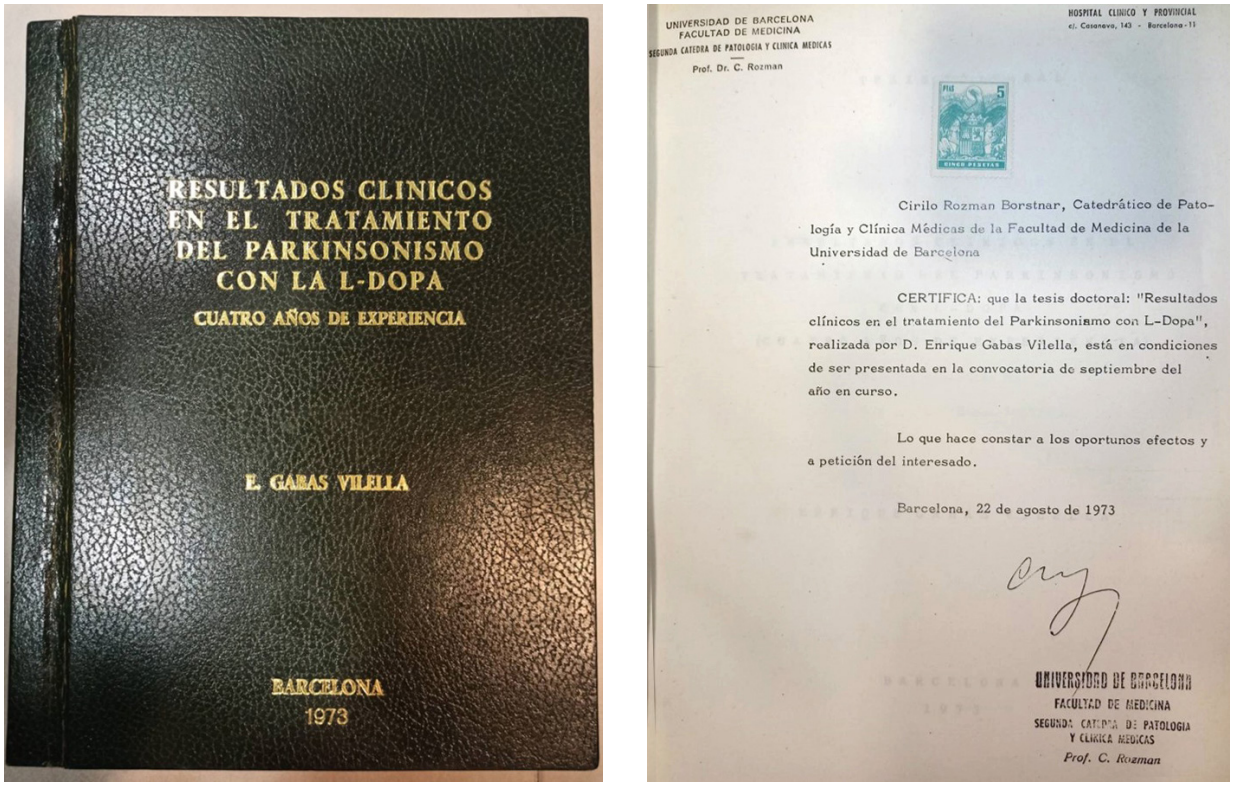


Figure 1. Title page of Enrique Gabàs Vilella's doctoral thesis.[33]

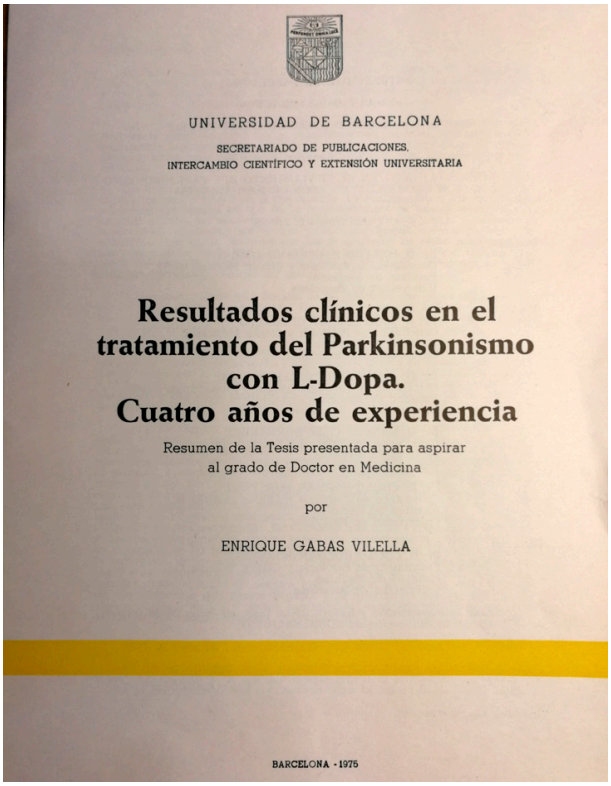
anorexia, and hyperkinetic involuntary movements. Codina also describes the experience of Calne et al.[28] in 20 patients with post-encephalitic parkinsonism (with less satisfactory results than those of Cotzias[15]), as well as the experience of Tissot et al.[20] in 20 patients with Parkinson's disease treated with L-DOPA plus a DOPA-decarboxylase inhibitor (Ro 4-4602), with spectacular results overall, some cases of apparent resolution, and far fewer adverse reactions than those reported by Cotzias[15] and Calne.[28] He concludes his review by suggesting that, should subsequent studies confirm the positive results of those mentioned previously, levodopa would emerge as "an effective therapeutic weapon to fight Parkinson's disease, particularly with regard to akinesia," proving to be superior to the medications and stereotactic surgical procedures available at the time.

The first study into levodopa in Catalonia and the rest of the Iberian Peninsula was conducted by Dr Enrique Gabàs Vilella (in Catalan, Enric Gabàs i Vilella) and Dr Adolfo Ley Gracia, and was started in April 1969. Ley and Gabàs reported their experience at the Spanish Society of Neurology's Annual Meeting in Barcelona on 12 December 1969, and published their findings in the 54th volume of *Medicina Clínica*, in 1970.[29]

Dr Enrique Gabàs was a neurosurgeon at Hospital Vall d'Hebron in Barcelona. During his residency at Hospital Clínic i Provincial de Barcelona (1968-1971), and under the direction of his mentor, Dr Adolfo Ley, he began to study the effects of levodopa on private patients from Ley's San José Clinic and patients attended at the neurosurgery department of Hospital Clínic, led by Ley, where Gabàs specialised in neurosurgery. The therapeutic resources available for Parkinson's disease at the time were very limited, with the exception of stereotactic surgery for tremor.[30-32] Enrique Gabàs and Adolfo Ley had to overcome huge obstacles. Firstly, the difficulty of obtaining levodopa during the Franco dictatorship; they managed to procure the drug first from Switzerland

and later through F.H.E.R. Pharmaceuticals (which subsequently marketed the drug under the brand name Dopalfher®).[33] In April 1969, they began administering levodopa to patients with this disabling disease, confirming the positive results reported in the United States and Canada. Gabàs first reported his encouraging results at the Spanish Society of Neurology's Annual Meeting in Barcelona on 12 December 1969, and in 1970 published the study "Resultados de nuestros primeros ensayos con L-DOPA en el tratamiento de los síndromes parkinsonianos" (results from our first trials with L-DOPA in the treatment of parkinsonian syndromes).[29] He described his experience with six patients with Parkinson's disease: a 59-year-old woman who had undergone left thalamotomy seven years earlier, and five men aged 68, 64, 55, 59, and 64 years, all of whom had Parkinson's disease with progression times between six months and 19 years. All patients were treated with L-DOPA at 300 mg/day in three doses, increasing by 300 mg every two days until reaching an optimal dose of 3-5 g/day. Results were favourable in all patients, and the results in the patient with 19-year history of Parkinson's disease were described by the authors as "spectacular."

Enrique Gabàs[33,34] continued with his research for a further four years, subsequently defending his doctoral thesis in 1973 (Figures 1 and 2). Gabàs expanded his series to 50 patients (18 women and 32 men aged 42-82 years) with parkinsonism (idiopathic in 34, post-encephalitic in 14, and vascular in one, plus one case of bilateral calcifications in the basal ganglia). The patients treated by Gabàs presented disease progression times ranging from six months to 35 years, with the disease manifesting between the ages of 30 and 40 in 2% of patients, between 40 and 50 years of age in 22%, between 50 and 60 in 44%, between 60 and 70 in 28%, and between 70 and 80 in 4%. Nine patients had undergone unilateral stereotactic surgery (thalamotomy in seven and pallidotomy in two). Based on the dosage used by Cotzias et al.,[15] Gabàs administered 1.5 g/day of levodopa in three doses of 500 mg, increasing the dose to 7-8 g/day on a case-by-case basis. Six patients received levodopa plus a DOPA-decarboxylase inhibitor, Ro 4-4602, provided by Hoffmann-La Roche for clinical research (trial Ro 8-0576). Patients underwent neurological examination with a particular focus on tremor, rigidity, and akinesia (scored from 0 to 4); writing for one minute (Figure 3); number of times the patient was able to open and close the hands in one minute; number of buttons the patient was able to button and unbutton in one minute; number of steps needed to walk 10 metres; and recordings of speech and video footage recorded before treatment, at 2, 3, and 6 weeks of treatment, and at 6, 18 (25 patients), and 48 months (18 patients) of treatment. Patients also underwent electromyographic studies before treatment and once the initial period had concluded (Figure 4). Patients displayed marked improvements, particularly in akinesia, but also in rigidity and tremor; these results were consistent with those reported by the North American researchers. In the initial phase of treatment, 12% were clinically cured, 22% achieved excellent improvements, 32% presented good improvements, 18% displayed moderate improvements, and 10% presented minimal or no improvement. At 14 months of treatment, Gabàs observed a tendency to deterioration. However, improvements persisted in the long term: at 18 months, 30% of patients presented sustained improvements as compared to baseline, 11.5% displayed little improvement, 11.5% had discontinued


UNIVERSIDAD DE BARCELONA

SECRETARIADO DE PUBLICACIONES,
INTERCAMBIO CIENTÍFICO Y EXTENSIÓN UNIVERSITARIA

Resultados clínicos en el tratamiento del Parkinsonismo con L-Dopa. Cuatro años de experiencia

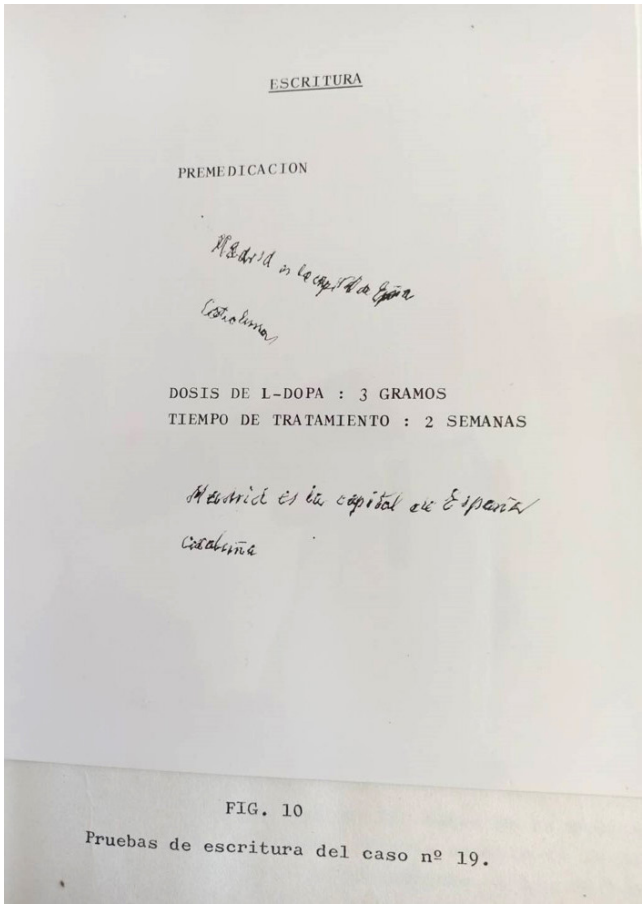
Resumen de la Tesis presentada para aspirar al grado de Doctor en Medicina

por

ENRIQUE GABAS VILELLA

BARCELONA - 1975

Figure 2. Title page of Gabàs Vilella's book on his own doctoral thesis.[34]



ESCRITURA

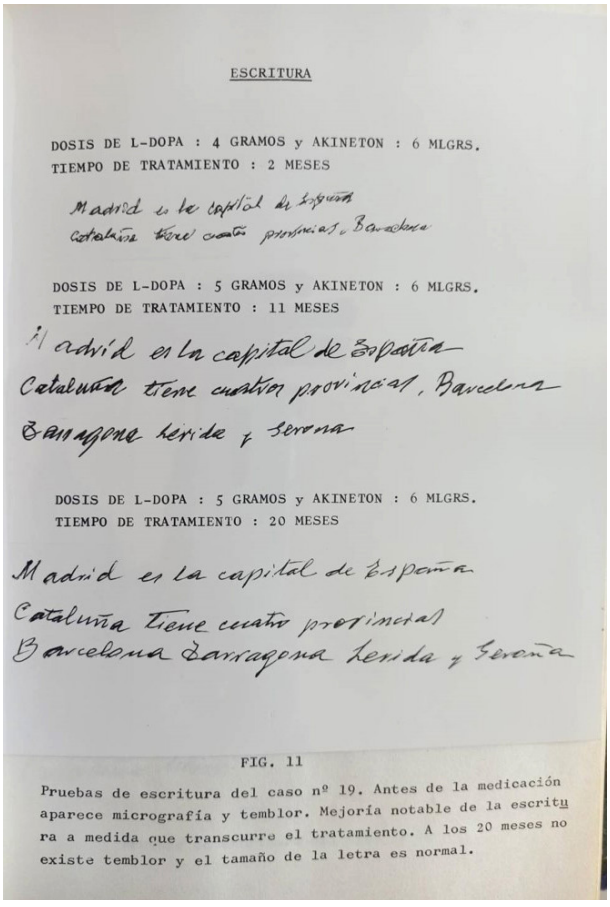
PREMEDICACION

Madrid es la capital de España
Cataluña

DOSIS DE L-DOPA : 3 GRAMOS
TIEMPO DE TRATAMIENTO : 2 SEMANAS

Madrid es la capital de España
Cataluña

FIG. 10
Pruebas de escritura del caso nº 19.



ESCRITURA

DOSIS DE L-DOPA : 4 GRAMOS y AKINETON : 6 MLGRS.
TIEMPO DE TRATAMIENTO : 2 MESES

Madrid es la capital de España
Cataluña tiene cuatro provincias, Barcelona

DOSIS DE L-DOPA : 5 GRAMOS y AKINETON : 6 MLGRS.
TIEMPO DE TRATAMIENTO : 11 MESES

Madrid es la capital de España
Cataluña tiene cuatro provincias, Barcelona
Tarragona Lerida y Gerona

DOSIS DE L-DOPA : 5 GRAMOS y AKINETON : 6 MLGRS.
TIEMPO DE TRATAMIENTO : 20 MESES

Madrid es la capital de España
Cataluña tiene cuatro provincias
Barcelona Tarragona Lerida y Gerona

FIG. 11
Pruebas de escritura del caso nº 19. Antes de la medicación aparece micrografía y temblor. Mejoría notable de la escritura a medida que transcurre el tratamiento. A los 20 meses no existe temblor y el tamaño de la letra es normal.

Figure 3. Recording of handwriting (1 minute). Case 19, before treatment and at two weeks and two, 11, and 20 months of treatment. Source: Gabàs Vilella.[33]

treatment, 21% had died, and the remaining 26% were lost to follow-up. The most frequent adverse reactions were gastrointestinal alterations. Hyperkinesia was a "fearsome" adverse reaction, and confusional states and psychomotor agitation were also considered severe secondary effects of the drug. Based on his four-year experience with L-DOPA in 50 patients with parkinsonian syndromes, Gabàs concluded that the drug may be indicated for all patients with parkinsonism, regardless of clinical type (although he did observe that patients with post-encephalitic parkinsonism worsened in the long term), sex, age, or disease progression time. He also concluded that the drug was generally well tolerated, although treatment must be started at low doses and increase progressively. According to his experience, the first symptom to improve was akinesia, followed by rigidity and, to a lesser extent, tremor. Such neurovegetative symptoms as sialorrhoea and hyperhidrosis also improved with L-DOPA. Gabàs supported the combination of L-DOPA with a DOPA-decarboxylase inhibitor, particularly in patients presenting severe adverse reactions (hyperkinesia and psychiatric disorders), and warned that the most frequent adverse reactions were gastrointestinal alterations (present in 96% of cases), although these were mild and transient.

With the pioneering experience of Enrique Gabàs and Adolfo Ley, the use of L-DOPA quickly spread in Barcelona and Catalonia, and their results were subsequently corroborated by the Madrid school of Dr Sixto Obrador. In Barcelona, Espadeler et al.[35] published their experience in 20 patients, reporting

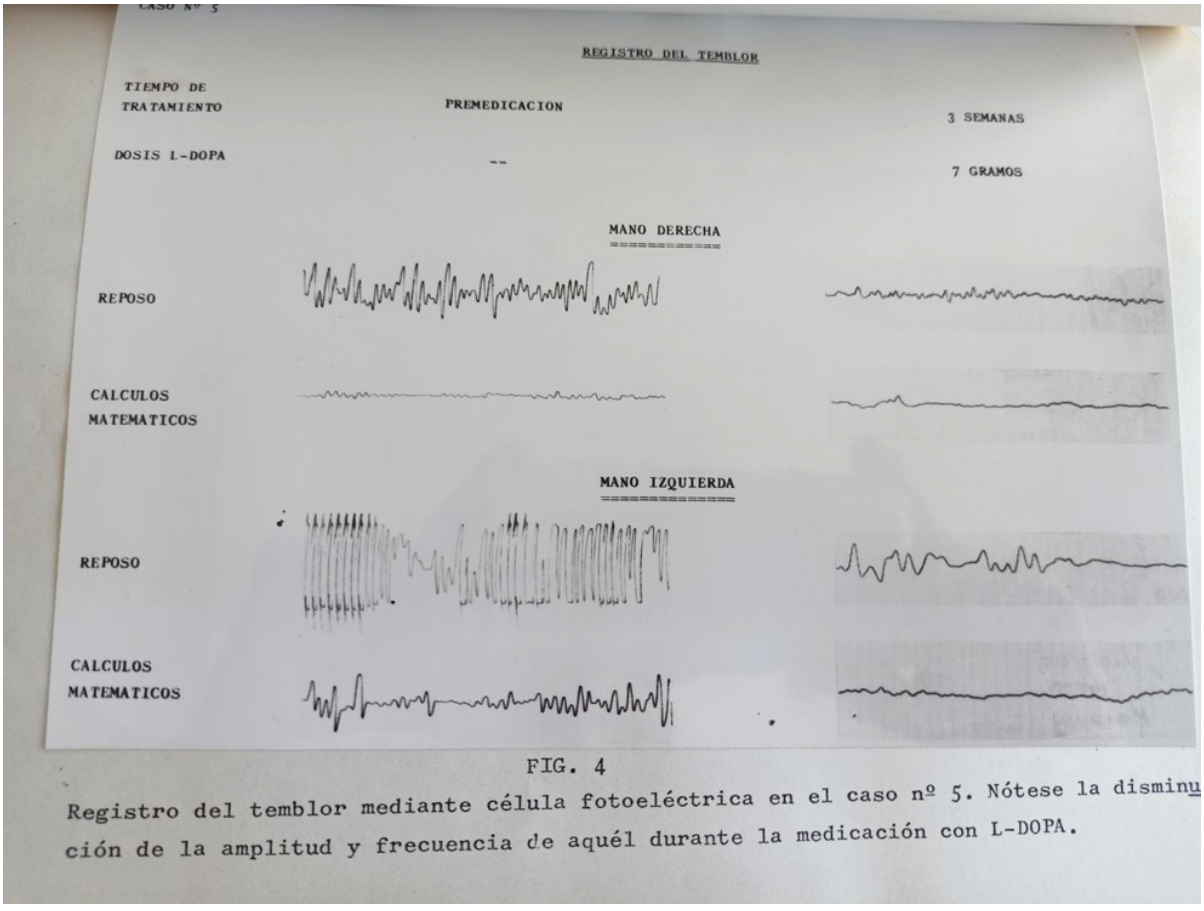


Figure 4. Recording of tremor. Case 5, before treatment and at three weeks of treatment. Source: Gabàs Vilella.[33]

optimal results in 20% of cases, good results in 35%, and moderate results in 40%. The first experiences with L-DOPA in Madrid were published in April 1971 by Peraita, Giménez-Roldán, and Zafra,[36] who treated 24 patients with 4-10 g/day and prospectively studied 16 of them, evaluating a battery of 18 signs and symptoms of the disease: tremor, bradykinesia (finger-counting), dysdiadochokinesia, fine movements (bringing a glass to the mouth), gait, writing the name of the hospital, posture, time taken in seconds to climb a flight of stairs, cogwheeling, speech, drawing a spiral, standing up from a chair, sialorrhoea, seborrhoea, swallowing, physical disability (level of dependence), akathisia, and masked facies (severity scored 1-3). Patients presented improvements in all areas, ranging from 14% to 85%, with less marked improvements in tremor (29.1%) and greater improvements in standing up from a chair (75%), bringing a glass to the mouth (70.5%), and bradykinesia (55.3%); these results were consistent with those reported in previous studies. At the same time in the Basque Country, Figuerido and de la Herrán, of the Hospital Cruz Roja de Bilbao neuropsychiatry department, reported their first clinical experience with L-DOPA in a lecture at the Bilbao Academy of Medical Sciences on 21 November 1969, and subsequently published an article with their conclusions in issue 119 of *Revista Clínica Española* on 31 December 1970.[37] They explored the application of L-DOPA (mean dose of 500 mg/day) combined with a monoamine oxidase inhibitor (which slows the breakdown of dopamine and its metabolism to methoxytyramine and homovanillic acid), isocarboxazid (Marplan), at a mean dose of 10 mg/day, reducing the

Sábado, 21 de noviembre de 1970 NOTICIAS MEDICAS Página 25

«LA L-DOPA ES EL FARMACO MAS EFICAZ DE QUE DISPONEMOS HOY DIA»

Entrevista con el Doctor Codina Puiggrós

La L-Dopa vino a incrementar el número de sustancias empleadas en el tratamiento sintomático de la parálisis agitante o enfermedad de Parkinson. Entrevistamos al doctor don Agustín Codina Puiggrós, para que, como especialista en dichos tratamientos, nos hable de la eficacia experimentada por la L-Dopa en esos terrenos.

—Según su opinión, ¿es la L-Dopa el tratamiento idóneo para la enfermedad de Parkinson?

—No existe, en la actualidad, tratamiento apropiado para esta enfermedad. Sin embargo, sí que puede considerarse esta droga como una medicación que mejora de forma ostensible la enfermedad de Parkinson. Y, sin duda, constituye, en términos generales, *el fármaco más eficaz que disponemos hoy día.*

—¿Qué grado de toxicidad tiene?

—La L-Dopa no está exenta de efectos secundarios, pero pueden reducirse a un mínimo tolerable por el enfermo y con frecuencia pueden obviarse si la droga se maneja debidamente. Por orden de frecuencia hay que señalar la anorexia y la náuseas que sobrevienen, ...

... frecuencia, el paciente *prefiere tener hipercinesias, sino son intensas, que la molesta e incapacitante hipocinesia.* Su mecanismo de producción no es bien conocido y el estudio del mismo se presta a consideraciones muy sugestivas tales como que la presunta saturación de Dopamina ya aludida permitiría la puesta en marcha de vías hiperkinético-productoras o que la desaparición de la akinesia haría posible la presentación de hipercinesias enmascaradas por aquélla.

Con mucha menor frecuencia, y con dosis altas, pueden sobrevenir manifestaciones psíquicas que remiten al descender la posología. Cabe advertir, finalmente, otros efectos secundarios, poco frecuentes y de poca importancia: aumentos transitorios de las cifras de urea en sangre y de las transaminasas glutamicooxalacéticas.

La enumeración de los efectos secundarios ...

- «TIENE COMO VENTAJA FUNDAMENTAL EL NOTABLE EFECTO BENEFICIOSO QUE EJERCE SOBRE LA HIPOKINESIA»
- «CONSTITUYE UN HITO FUNDAMENTAL EN LA ENFERMEDAD DE PARKINSON, PUES ES UN MEDICAMENTO CON BASE PATOGENICA»

ciosos conseguidos por los dos grupos fueron
más bien medianos. Ello explica que posterior-
mente otros autores (Greer y Williams, 1963;
Fehling, 1966) utilizando la droga que nos
ocupa pusieron en duda su eficacia. Hay que
tener en cuenta que en estas primeras expe- ...

... pírica el tratamiento de la enfermedad de Parkinson con extractos de las solanáceas. Posteriormente se emplearon los alcaloides de las solanáceas, especialmente la atropina y la escopolamina. Y, en 1946, se utilizaron los atropínicos de síntesis que han sido los pre- ...

Figure 5. Interview with Dr A. Codina: "L-DOPA is the most effective drug currently available." Press clipping dated 21 November 1970, kept by Dr E. Tolosa (provided by Dr E. Tolosa).

therapeutic dose of L-DOPA. Their sample included 32 patients with primary or idiopathic Parkinson's disease, who were treated for five months. Figuerido and de la Herrán reported great improvements in amimia and akinesia during the first month of treatment, and subsequently in rigidity; tremor also improved, although to a lesser extent, at three months of treatment. However, they warned about the risk of hypertensive crises associated with the treatment.

Conclusions

Levodopa brought about a radical change in the management of Parkinson's disease and in neurology itself. Prior to its development, patients with Parkinson's disease were normally attended by neurosurgeons. In Catalonia, in the 1960s, neurosurgeons with a special interest in stereotactic surgery included Dr Fabià Isamat de la Riva, a physician at Hospital Sagrat Cor in Barcelona and a student of Irving Cooper's in New York; Dr Adolfo Ley of Hospital Vall D'Hebron; and Dr Jaume Vilató of Hospital del Mar. Therefore, it should come as no surprise that neurosurgery schools pioneered the use of levodopa. In Barcelona, the school of Dr Adolfo Ley, and particularly Dr Enrique Gabàs, conducted the first studies with levodopa, replicating the excellent results reported by Cotzias.[15] After the drug was marketed in the 1970s, its use was consolidated and expanded by neurologists. In Barcelona, the neurologists pioneering the use of levodopa were Dr Lluís Barraquer Bordas and Dr Josep Maria Grau Veciana at Hospital de la Santa Creu i Sant Pau, Dr Agustí Codina (Figure 5) and Dr Francesc Miquel at Hospital Vall d'Hebron, and Dr Carles Oliveras de la Riva, Dr Adolf Pou, and Dr Ignasi de Gispert i Cruz at Hospital Clínic. Thanks to the efficacy of levodopa, functional surgery was no longer indicated for patients with Parkinson's disease by 1975.[38] Surgical treatments were abandoned for many years before re-emerging in the 1990s due to technical advances and a deeper pathophysiological understanding of the disease.

Conflicts of interest

No funding was received for the present study.

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