Homage to Paula Coutinho – a pioneer in Portuguese and worldwide neurogenetics

Homenagem a Paula Coutinho – uma pioneira da neurogenética portuguesa e mundial

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SUMMARY

This is a tribute to an outstanding Portuguese neurologist and researcher, Paula Coutinho (1941-2022), who specialized in the care and study of people with familial amyloidotic polyneuropathy and Machado-Joseph disease which she helped define. As a result, she collaborated with the inauguration of the Centro de Estudos de Paramiloidose Antônio Rodrigues de Mello (CEPARM) founded in 1984 at the University Hospital of the Federal University of Rio de Janeiro. Since then, we admire her commitment to science and patients.

Keywords: Genetics; Amyloidosis, Hereditary, Transthyretin-Related; Machado-Joseph Disease; Portugal

RESUMO

Esta é uma homenagem a uma notável neurologista e pesquisadora portuguesa, Paula Coutinho (1941-2022), que se especializou no cuidado e estudo de pessoas com polineuropatia amiloidótica familiar e doença Machado-Joseph, que ela ajudou a definir. Como resultado, colaborou com a inauguração do Centro de Estudos de Paramiloidose Antônio Rodrigues de Mello (CEPARM) fundado em 1984 no Hospital Universitário da Universidade Federal do Rio de Janeiro. Desde então, admiramos o seu compromisso com a ciência e os pacientes.

Palavras-chave: Genética; Amiloidose Hereditária Relacionada à Transtirretina; Doença de Machado-Joseph; Portugal

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INTRODUCTION

Paula Mourão do Amaral Coutinho (August 10, 1941 – June 11, 2022)[8], figure 1, translates several personality traits of the Portuguese people: the pioneering spirit extols in "Os Lusiadas" by Luís de Camões when referring to "Por mares nunca dantes navegados" - "By seas never sailed before", about the Discoveries and the strength of the Great Navigators; the way to be reserved, polite and kind. Thus, from the Náutica Escola de Sagres, these navigators piloted their ships with dexterity and good use of instruments to locate and follow their course, and nowadays the Portuguese Paula Coutinho, to carry out her plan, knew and deeply loved her mission.

Paula Coutinho devoted herself above all to the practice and teaching of neurology, neurogenetics and neuroepidemiology and, mainly, to the study of people with familial amyloid polyneuropathy / Transthyretin amyloid polyneuropathy (ATTR-PN) and Machado-Joseph Disease (MJD) / spinocerebellar ataxia 3 (SCA3), and their clinical, neuropathological and epidemiological characterization.

Figure 1. Paula Coutinho (1941-2022). Adapted from http://avozdecambra.pt/?p=5969.

CAREER AND POSITIONS

Paula Coutinho worked at the Neurology Service of the Hospital Geral de Santo António, Porto/Pt, since August 1966, as a grantee from the Calouste Gulbenkian Foundation, in the application of immunofluorescence to familial amyloidotic polyneuropathy. She was also an intern, general intern, "complementary intern", specialist, assistant, and head of clinic and service at this Hospital (1967-1998)[5,8] .

In between, she was an assistant in neuropathology at the Institute of Pathology at the University of Geneva (1971-1972) and in neurology at the Cantonal Hospital of Geneva (1973-1974)[5,8] .

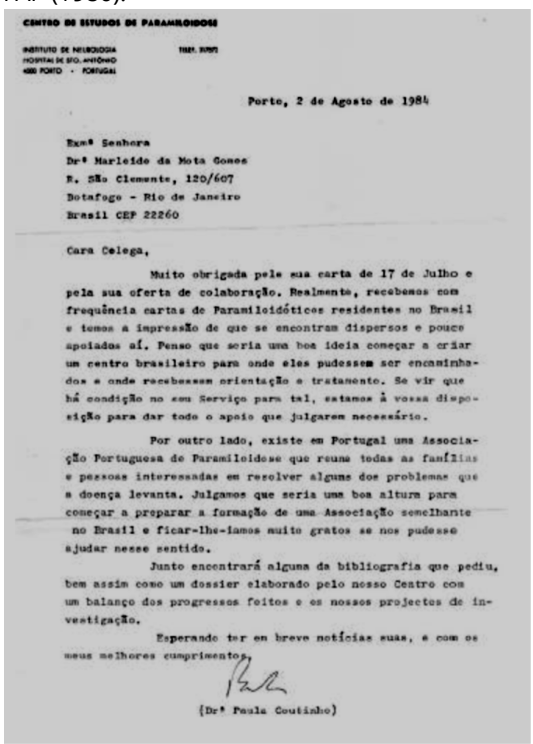
She was also a clinical consultant at the Center for the Study of Paramyloidosis, Porto (1975-1992), besides being an invited professor of neurology at the Abel Salazar Institute of Biomedical Sciences (1979-1998)[5,8] .

Subsequently, she founded the Neurology Service of the new Hospital of São Sebastião, Santa Maria da Feira, in 1999[8].

At the University of Porto, she was also part of the research team from the beginning (1992) of the Unidade de investigação Genética e Epidemiológica em Doenças Neurológicas, which would later be installed at the Instituto de Biologia Molecular e Celular (IBMC), now part of the Instituto de Investigação e Inovação em Saúde. She was also a member of the clinical team at the Centro de Genética Preditiva e Preventiva, IBMC[5,8] .

DISEASES MAINLY STUDIED

Regarding the ATTR-PN, Mário Corino da Costa Andrade (June 10, 1906-June 16, 2005) pioneered its description in a group of Portuguese families, as published in 1952. Many others with similar manifestations have been reported worldwide, and in the wake of the great master, the remarkable Paula Coutinho emerged. As for the profile of this disease, it is due to a dominant mutation (V30M) in the TTR gene and amyloid deposits in the extracellular matrix of different tissues that is expressed in adulthood mainly by progressive sensorimotor polyneuropathy and autonomic neuropathy with cardiomyopathy and gastrointestinal symptoms[4]. It is also remarkable that the disease is classically classified into three stages what is known as the Coutinho stages of ATTR-FAP (1980).



CENTRO DE ESTUDOS DE PARAMILOIDOSE

Porto, 2 de Agosto de 1984

Exmª Senhora
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Cara Colega,

Muito obrigada pela sua carta de 17 de Julho e pela sua oferta de colaboração. Realmente, recebemos com frequência cartas de Paramiloidóticos residentes no Brasil e temos a impressão de que se encontram dispersos e pouco apoiados aí. Penso que seria uma boa ideia começar a criar um centro brasileiro para onde eles pudessem ser encaminhados e onde recebessem orientação e tratamento. Se vir que há condição no seu Serviço para tal, estamos à vossa disposição para dar todo o apoio que julgarem necessário.

Por outro lado, existe em Portugal uma Associação Portuguesa de Paramiloidose que reune todas as famílias e pessoas interessadas em resolver alguns dos problemas que a doença levanta. Julgamos que seria uma boa altura para começar a preparar a formação de uma Associação semelhante no Brasil e ficar-lhe-iamos muito gratos se nos pudesse ajudar nesse sentido.

Junto encontrará alguma da bibliografia que pediu, bem assim como um dossier elaborado pelo nosso Centro com um balanço dos progressos feitos e os nossos projectos de investigação.

Esperando ter em breve notícias suas, e com os meus melhores cumprimentos,

(Drª Paula Coutinho)

Figure 2. Initial contact letter for the creation of a Brazilian research and patient care Center in a University Hospital for those with Corino Andrade's Familial Amyloid Polyneuropathy.

Paula Coutinho's partnership with Corino Andrade, who officially retired in 1976, lasted because in 1975 the Portuguese health authorities asked him to investigate a new disease, and Paula Coutinho accompanied him to the Azores for this purpose. This enterprise resulted in the 1978 account of the clinical features of all identified patients, having recognized the continuing clinical expression of this disorder and proposition that the Machado, Thomas and Joseph families had the same genetic condition. Paula Coutinho summarized in her doctoral thesis on MJD her participation in the individualization of this disease by saying that "I witnessed the first steps of exploration of Machado-Joseph disease, I collaborated in its clinical definition, genetic and pathological, I helped name it, accompanied its identification in other parts of the world, participated in the first attempts to establish it as a distinct nosological entity."[2]. In sum, MJD is the most common subtype of autosomal dominant cerebellar ataxia type 1. It was first described in Azorean descendants, and also recognized in Brazil, mainly in its South region. It has been associated with a mutation of the MJD1 gene on chromosome 14, and its clinical features include progressive ataxia, dysarthria, postural instability, nystagmus, eyelid retraction, and facial fasciculations. Paula Coutinho described in her thesis (1992) the phenotype and evolution of three major sub-phenotypes called by her, types 1, 2 and 3[3]. Regarding the landmark of the study of MJD and her thesis, “Machado-Joseph Disease: tentative definition”, she won the first edition of the Bial Prize (1993).

Furthermore, the importance of her participation in the systematic, population-based Portuguese screening of hereditary ataxias and spastic paraparesis, for more than 12 years, should be highlighted. This was unfolded in the clinical and genetic identification of several new forms of recessive (AOA1, AOA2, AOA4) and dominant ataxias (SCA37), as well as several new loci and genes for spastic paraplegias[2,3,8] .

Paula Coutinho, in addition to studying these patients, contributed substantially to improving their well-being, the driving force of the opening, in 1984, of a Brazilian center dedicated to the care and research of patients with ATTR-PN (see figure 2), denominated by MMG of Centro de Estudos de Paramiloidose Antonio Rodrigues de Mello (Antonio Rodrigues de Mello Paramyloidosis Study Center) in homage to the neurologist who coined the internationally known term of Corino Andrade's familial amyloidotic polyneuropathy. By April 1985, CEPARM had registered six patients and another 24 were referred by the Portuguese Center for Paramyloidosis. Among the first patients was the princeps case, Mr Antonio, from another hospital where MMG also worked, who promoted her initial connection with the Portuguese Center for Paramyloidosis and Paula Coutinho. In the year following the organization of this Center, MMG went on to do a master's degree at MacMaster University-Ca and then worked at the Ministry of Health-Brasília-Br, being replaced in the coordination of CEPARM for a short period by Charles André, MD, PhD, and soon after the final coordination fell to MWC. Many more patients have been treated over the nearly four decades of CEPARM's existence, predominantly under the guidance of MWC, most from the Southeast-Br region, and several have received cutting-edge therapies in international clinical trials. It should be noted that the vast majority of early CEPARM patients came from Rio de Janeiro, which indicates the predominance of Portuguese immigration from the Iberian Peninsula, from Póvoa do Varzim to this State. On the contrary, in the south of Brazil, especially in Santa Catarina, the patients registered by other Brazilian authors are predominantly those with MJD, also of Portuguese origin, but Azorean, likewise studied by researchers Corino Andrade and Paula Coutinho[4].

More recently, a study with the participation of MWC estimates that there are around 5,000 people with ATTR-PN in Brazil, considering that Portuguese descendants in this country are more numerous than those in the country of origin, endemic for ATTR-PN. Thus, the clinical-epidemiological work of Paula Coutinho was extremely important in highlighting the relevance of this disease from a human-medical-scientific point of view also in Brazil[7]. Reference should be made to the continuity of the work of Paula Coutinho by Teresa Coelho of the Portuguese Paramyloidosis Center who head the study "Paramyloidosis in Portugal and the world: from a fatal disease to chronic disease with preserved quality of life", winner of Bial Prize for Clinical Medicine (2020). This leader has encouraged the work of MWC at CEPARM[6].

THE BACKSTAGE AND CLOSING

A few years after the CEPARM inauguration, MMG and MWC had the opportunity to personally meet the Pioneer at the 14th Brazilian Congress of Neurology, in Rio de Janeiro, held from September 22 to 27, 1990, under the direction of Sergio Novis, also head of Neurology Service of the University Hospital where the CEPARM transdisciplinary team worked. Later, in 1992, MMG visited Paula Coutinho at the General Hospital of Santo António, Porto/PT, in the Neurology Service. At that time, there was a meeting in a restaurant with a panoramic view of the Douro River, when the great Portuguese spoke about the history of traditional local dishes.

Paula Coutinho was cultured, sensitive and humble, having a friendly relationship with Brazilian neurologists such as those who study paramyloidosis and admire the Portuguese saga, and she also appreciated the poems of Manuel Bandeira, the preferred author of everyday and melancholic themes, having she ordered this bard's books from MMG.

For the past five years, Paula Coutinho has lived in a nursing home, and regretfully, the respected and kind person passed away on June 11, 2022, at the age of

79, in the city of Porto, Portugal. However, her legacy and example are indelible in the history of neurology, and she too will be remembered fondly by those with whom she came in contact.

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