CASE REPORT

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Machado-Joseph Disease, A Case Report of Treatment Based on Phototherapy

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ABSTRACT

Machado-Joseph disease (MJD) is a rare autosomal dominant disease caused by a mutation in exon 10 of the *ATXN3* gene resulting from a cytosine-adenine-guanine trinucleotide repeat. A case of a 48-year-old man with MJD is reported. His father, two paternal aunts, and his older sister all died because of this disease, and his younger brother had the same disease. Due to the absence of therapeutic options, phototherapy sessions were offered as an alternative between 425 and 650 nm 1.33 Joules/cm^2, 30 cm above the chest. After three months of phototherapy sessions, the following items showed a decrease in their scores: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, and general health. The only variable that remained unchanged was pain. He discontinued treatment, attributed the deterioration to phototherapy. A year later, as the disease progressed, he decided to resume the same scheme, and the following trends were observed: a) Improvement in role limitations due to physical health, emotional well-being, social functioning, and general health; b) No changes in role limitations due to emotional problems and pain and c) deterioration in energy/fatigue.

Keywords: Palliative care, phototherapy, spinocerebellar ataxia type 3

INTRODUCTION

Machado-Joseph disease (MJD), also known as spinocerebellar ataxia type 3 (SCA3), is a hereditary and multisystem neurodegenerative disease belonging to the group of spinocerebellar ataxias, which are diseases characterized by degeneration of the pyramidal, extrapyramidal, oculomotor, and cerebellar systems, in addition to motoneurons [1]. Approximately 40 subtypes of ataxias have been classified, of which SCA3 is the most common subtype globally [2]. Clinically, it is found to be heterogeneous even among family members (peripheral neuropathy, dystonia, ophthalmoplegia, parkinsonism, cerebellar ataxia, non-motor manifestations, cognitive impairment, sleep disorders, olfactory dysfunction, and psychiatric symptoms), but progressive in all [3]. The first neurological involvement occurs at the level of coordination of extremities, control of voluntary movements, speech, walking, and swallowing. Moreover, with the course of the disease, clinical findings in the pyramidal, extrapyramidal, peripheral, and cranial nerves will be noted, reducing the life expectancy to approximately 21 years from the beginning of the clinical picture. Although this disease has a variable onset and can begin in adolescence to old age, its onset is commonly observed in adulthood [4].

MJD was first classified by neurologist Coutinho and Sequeiros [5] among Machado-Joseph families who were inhabitants of the Azores islands. This autosomal dominant disease is a rare genetic pathology that is caused by a mutation in exon 10 of the *ATXN3* gene due to the repeat of a cytosine-adenine-guanine (CAG) trinucleotide [6] located on chromosome 14q32.1, which is a gene that, in the absence of its correct functioning, leads to the translation of an abnormal expansion of polyglutamine (polyQ) in the gene product (ataxin-3) and incorrect protein folding, resulting in alterations in different cellular processes and neuronal dysfunction and death. After the toxic aggregation of the protein, ataxin-3 with the abnormal expansion of the polyQ sequence neuronal inclusions is aggregated, promoting neuronal toxicity and degeneration [7].

The accumulation of toxic ataxin 3 comprises a C-terminal region and domain where an abnormal expansion of the polyglutamine tract occurs. This protein, in turn, binds to the specific intracellular calcium channel InsP3R1, thereby increasing its release. Excess intracellular calcium can kill cells by inducing

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cytotoxic processes, such as oxidative stress, mitochondrial permeability, and calpain activation [8]. Furthermore, loss of neurons occurs in the neostriatum and cerebellar cortex, whereas gliosis occurs in the spinal and cranial motor nuclei, substantia nigra, and cerebellar dentate nucleus. The presence of these aggregates in axons can negatively affect axonal transport mechanisms and result in neuronal degeneration [9]. Pathological ataxin-3 tends to aggregate as part of its natural function [10].

Unfortunately, to date, no specific cure for this pathology has been established, and this has urged doctors to seek alternative treatments, such as phototherapy, which has shown favorable treatment outcomes for other diseases of the central nervous system [11].

CASE PRESENTATION

The study investigated a 48-year-old man with MJD. His father, two paternal aunts, and older sister died from this disease. His younger brother also has the same affection. In this case, the disease manifested when the patient was 37 years old and compromised the mobility of his left ankle. Subsequently, several symptoms and signs of the disease progressively manifest in the patient (Table 1). Due to the absence of therapeutic options, phototherapy sessions were offered.

With the patient in the supine position, the phototherapy lamp (Federal Ministry of Health registration number: 1694E95) was turned on within a range between 425 and 650 nm, 11.33 Joules/cm^2, and 30 cm above the chest, following the next scheme: (a) 30-min daily sessions from Monday to Friday. The reason for the lamp's position above the thorax is that blood is a highly conductive material, and the lamp near the chest may increase the likelihood of energy reaching the aorta where the greatest systemic effect would occur by interacting with a high blood volume. Furthermore, the patient refused to undergo any laboratory tests.

Table 1. Clinical characteristics of the patient

Affected organ	Clinical characteristics
Ocular	Diplopia
Psychological	Depression
Sleep disorders	Obstructive sleep apnea
	Staggering or ataxic gait Progressive gait imbalance Uncoordinated body movements Increase in the support base Unsafe gait Clumsiness in movements
Facial	Difficulty swallowing and controlling saliva
Speaks	Impairment of normal speech with difficulty speaking
Muscular	Dystonia

The QR clarifies the actual status of the patient

The short form 36 health survey (SF-36) is a popular instrument for evaluating health-related quality of life in patients with several diseases and conditions [12]. The SF-36 measures eight dimensions: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health. For each dimension, the items were coded, aggregated, and transformed into a scale ranging from 0 (the worst health status for that dimension) to 100 (the best health status). Moreover, scores higher or lower than 50 indicate better or worse health status, respectively, than the average of the reference population. The component analyses revealed two distinct concepts measured by the SF-36: a physical dimension represented by the physical component summary and a mental dimension represented by the mental component summary. Moreover, this scale was registered in the patient before treatment and after 3 months, and it was repeated after 1 year.

After three months of phototherapy sessions, the following items were scored: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, and general health. The only variable that remained unchanged was pain. However, he discontinued treatment, attributed the deterioration to phototherapy.

A year later, as the disease progressed, he decided to resume the same scheme, and the following trends were observed: (a) improvement in role limitations due to physical health, emotional well-being, social functioning, and general health; (b) no changes in role limitations due to emotional problems and pain; and (c) deterioration in energy/fatigue and health changes (Table 2).

DISCUSSION

Although the age at onset of MJD is significantly varied (with extremes ranging from 4 to 70 years of age), the average age of onset is 32-40 years. The clinical presentation will begin to become progressive and disabling, with an average life expectancy of 20-25 years. In the present case, symptoms began at the average of the highest incidence in the world.

The abnormal repeat of the CAG trinucleotide tends to alter the *ATXN3* gene located on chromosome 14, in its fragment 32 of the short arm, and the protein ataxin-3, a soluble cysteine, weighing 42 kD, which is part of the cysteine-protease group with activity in the ubiquitin-proteasome system and participates in regulating protein degradation. Intracellular accumulation occurs in some parts of the brain. An excess of polyQ is also

Table 2. The 36 health survey questionnaire changes				
Parameter	**Date**			
	January 2023	**March 2023**	**January 2024**	**March 2024**
Physical functioning	70	50	35	30
Role limitations due to physical health	100	25	0	50
Role limitations due to emotional problems	100	66.7	66.7	66.7
Energy/fatigue	65	45	45	40
Emotional well-being	68	44	32	40
Social functioning	75	62.5	37.5	50
Pain	77.5	77.5	77.5	77.5
General health	60	40	15	35
Health change	75	25	25	25
This scale provides a profile of health status and is applicable to both patients and the general population. The scale goes from zero (the worst) to 100 (the best) in each dimension				

produced, creating a toxic environment for neurons and forming inclusions with the mutated protein ataxin-3, thereby resulting in MJD [7]. In the case of our patient's family, although several family members died from the same disease, no autopsy has been performed to corroborate intracellular accumulations.

The severity of abnormalities observed in the images depends on the length of the CAG repeats. Other studies, such as spect, are useful for observing certain abnormalities, such as the reduction in the density of the dopamine transporter in the striatum. In molecular diagnosis, different techniques are used to identify the main genes underlying MJD. It is important to differentiate MJD from other diseases because they share several similarities, such as autosomal dominant striatonigral degeneration, hereditary dentatorubral-pallidoluisian atrophy, and syphilis. In relation to this, it is crucial to insist with the patient to accept nuclear magnetic resonance imaging and other imaging studies of the central nervous system.

MJD is a progressive pathological condition with no specific treatment and varies symptoms. It responds in a limited way to symptomatic treatment. Unfortunately, since MJD is a rare and clinically heterogeneous pathology, it has not been possible to conduct double-linked clinical trials with controls and placebo. Currently, no proven treatment that can prevent SCA3, as well as other ataxias, has been established. Some experimental treatments include astragaloside IV, MJD1 deactivation, and interference with ribonucleic acid (RNA).

The average survival time of these patients was 21 years, with a range of onset of 7-29 years. In clinically confirmed cases of MJD, three groups of causes of death have been noted: neurological, respiratory, and enfectious diseases. Most patients die of pulmonary complications, usually within 6-29 years of onset, considering that no disease-modifying treatments have been established.

The case we present of application of phototherapy was in the absence of effective treatments that stop or cure cases of MJD and at the patient's request and applying the principle of "first do no harm" given the safety of phototherapy. However, it has not yet been determined whether the slowdown in disease deterioration was due to phototherapy, which requires a molecular explanation. Although the engineer who developed the lamp used with the patient based his work on the concept of isomerization of sugars such as those contained in RNA and deoxyribonucleic acid [13] and considering the evidence of the photobiomodulation effects on Messenger RNA [14], the role of phototherapy cannot be clearly attributed to the enflammatory cascade reduction (Figure 1) [15].

One of the limitations of this study was the lack of application of the following scales were not applied: the International

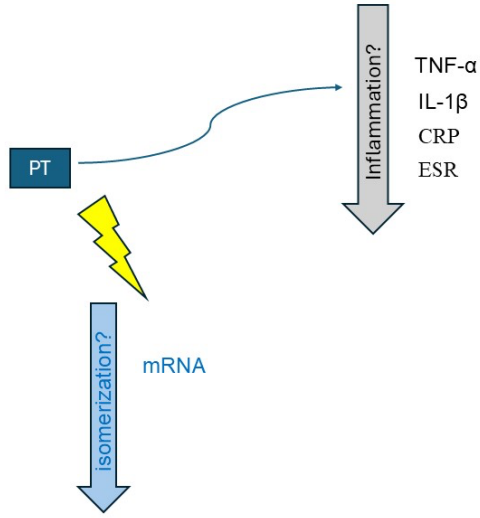

Figure 1. Possible actions of phototherapy on Machado-Joseph disease
CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IL: Interleukin, PT: Phototherapy, TNF-α: Tumor necrosis factor-α

Cooperative Ataxia Rating Scale and the Scale for the Assessment and Rating of Ataxia. However, the SF-36 documented clinical evolution stability, stopping the deterioration.

Ethics

Informed Consent: The patient written informed consent was obtained.

Footnotes

Authorship Contributions

Concept: H.M.Z., Design: H.M.Z., Data Collection or Processing: D.E.G.M., P.L.R., M.D.R.P., H.M.Z., Analysis or Interpretation: D.E.G.M., H.M.Z., Literature Search: D.E.G.M., P.L.R., M.D.R.P., H.M.Z., Writing: D.E.G.M., P.L.R., M.D.R.P., H.M.Z.

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