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Case Report

Relief of nocturnal neuropathic pain with the use of cannabis in a patient with Fabry disease

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ABSTRACT

Neuropathic pain is one of the most invalidating symptoms in patients with Fabry disease (FD), affecting their quality of life, it is linked to small fiber neuropathy and it may not respond to available disease specific treatments. We report the case of a 32 years old man with classic FD and severe neuropathic pain who, after the failure of several standard pharmaceutical approaches, was treated with medical cannabis with relief of nocturnal pain and sleep improvement.

1. Introduction

Anderson-Fabry Disease (FD), *OMIM* #301500 is a lysosomal storage disorder caused by the deficiency of the acid α-Galactosidase A (α-Gal) enzyme due to pathogenetic variants in the *GLA* gene located on the X-chromosome [1,2]. The enzyme deficiency results in progressive lysosomal accumulation of sphingolipids (mainly globotriaosylceramide, Gb-3 and globotriaosylsphingosine: Lyso-Gb3) into different body cells, particularly cardiomyocytes, kidney, neural and vascular endothelial cells, leading to a multi-organ damage [2,3]. Heterozygous females can be severely affected, although generally at a later age compared to hemizygous males [4].

The estimated prevalence of FD in the male population is 1:17.000–117,000 [5].

Clinically FD may present at any age; the classical form, identified in patients with very low or undetectable α-Gal activity, typically presents during childhood with manifestation such as extremity and abdominal pain, diarrhea, sweating abnormalities, recurrent fever, fatigue, cornea verticillata and angiocheratomas. Patients affected by the non-classic form, present with higher residual enzyme activity and usually have later manifestations that might affect a single organ [2,6,7]. In any case, during adulthood FD can lead to severe cardiac, renal, and cerebrovascular complications [8].

Currently two types of Enzyme Replacement Therapy (ERT) have been approved in EU: algasidase-beta and agalsidase-alfa. A pharmacological oral chaperone therapy (migalastat) has become more recently available for patients with amenable mutations [9].

Extremity pain, is one of the most invalidating symptoms in patients with FD, affecting their quality of life, since it may not respond to available specific disease treatments [10]. This neuropathic pain is a very common manifestation, affecting up to 81.4% of classical male patients and 65.3% of females, with a mean onset of 14.8 years for men and 19.8 years for women [11]. Two types of pain often co-occur in classical FD: chronic pain in hands and feet and severe episodic pain attacks known as “Fabry crises”. The chronic pain is often described as burning, shooting or tingling pain and can be enhanced by exercise, increased heat or fever [12]. The mechanisms involved in FD pain are complex and mainly related to small fiber neuropathy, probably caused by a dysfunctional perfusion of vasa nervorum due to Gb-3 accumulation [13]. The small fiber loss is higher in the distal long axons of the lower extremities [14]. Other mechanism such as inflammation and oxidative stress can contribute to Fabry neuropathy [15,16].

Analgesic drugs, so far used as first line treatments, includes tricyclic antidepressant such as amitriptyline, serotonine and noradrenaline reuptake inhibitors such as duloxetine; carbamazepine, gabapentin and pregabalin [17]. Unfortunately, many patients do not respond, and pain therapy in FD remains an unmet need [18]. The use of cannabinoids was mentioned in a recent review as a possible treatment for pain in FD, but clinical evidence of its possible effects is still lacking [19].

Here we describe, to our knowledge for the first time, a patient with classic FD with severe painful.

neuropathy successfully treated with cannabis after the failure of several analgesic approaches.

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2. Clinical case

A 29 years old man presented a clinical history compatible with classic FD: burning pain at hands and feet extremities from infancy, which worsened with physical exercise and/or fever episodes; frequent abdominal pain and diarrhea; heat intolerance and anhidrosis. He was referred to the Regional Coordinating Centre for Rare Diseases (RCCRD) of Udine by the general practitioner, together with his family.

Physical examination performed by the specialist at RCCRD showed periumbilical and scrotal angiokeratomas, confirming the strong suspect for FD.

The diagnosis of FD was then confirmed in the laboratory of the RCCRD by the presence of undetectable levels of α-Gal enzyme activity in leukocytes, and the identification of the pathogenetic variant c.466G > A p.(A156T) in the *GLA* gene.

Further laboratory and instrumental exams performed after diagnosis showed the presence of cornea verticillata, renal involvement with proteinuria (676 mg/24 h), and hyperfiltration (creatinine clearance 190.4 ml/min); initial cardiac involvement with hypertrophic interventricular septum (thickness 15 mm at magnetic resonance); presence of small fiber neuropathy (SFN) confirmed by skin biopsy.

The same pathogenic variant was found in his mother and his older brother. The mother, 59 years old, had cornea verticillata and cardiomyopathy but no acroparesthesiae; the brother, 32 years old, had cornea verticillata, angiokeratomas, proteinuria, chronic diarrhea, hyperhidrosis, burning pain at hands and feet from infancy only during fever.

Enzyme replacement therapy with algasidase-beta was started at a standard dosage of 1 mg/kg i.v. b.w. without side effects, together with olmesartan 10 mg/day.

After 1 year of treatment there was an improvement in kidney function (proteinuria 353 mg/24 h, creatinine clearance 116.1 ml/min), and normalization of cardiac interventricular septum (thickness 8 mm at ultrasound).

Nevertheless, severe burning pain at extremities persisted, influencing sleep and quality of life. Therefore, different pharmaceutical approaches were attempted over the 3 years following the diagnosis, without substantial results. In details: first gabapentin, then pregabalin, finally palmitoylethanolamide were prescribed by the neurologist and tried for several months without any positive effect on pain. Of note, the patient use to take paracetamol 1000 mg when needed for acute pain attacks, with partial benefit.

Finally, at the age of 32 years, the patient was referred to a pain management specialist and, in accordance with the metabolic team, after informed consent, therapy with medical cannabis in the form of oral Tetrahydrocannabidiol (THC) 8%, Cannabidiol (CBD) 12% 100 mg/die was started and then increased up to 500 mg/die. An improvement of pain, measured by the Brief Pain Inventory questionnaire (BPI) [20], without significant side effects, was reported after 1 month of treatment, and maintained after one year of treatment. As shown in Table 1, a particular decrease of pain interference with nocturnal sleep was recorded.

Table 1
Brief pain inventory scores (from 0 to 10) at baseline and follow up.

	Baseline	After 1 Month of Therapy	After 1 Year of Therapy
	Only paracetamol	Paracetamol + Cannabis	Paracetamol + Cannabis
Item			
Worst Pain	7	5	7
Least Pain	2	2	2
Average Pain	4	3	3
Current Pain	4	2	2
Pain Relief %	50	60	70
Pain Interference with General Activities	6	4	5
Mood	8	6	8
Walking Ability	4	5	3
Normal Work	4	4	3
Relation with other People	8	6	7
Sleep	**9**	**4**	**4**
Enjoyment of Life	10	7	9

3. Discussion

Neuropathic pain is one of the most invalidating symptoms of FD and its treatment is particularly challenging. It is usually characterized by localization in the extremities, burning sensation and early presentation in the classic forms, representing one of the hallmarks for the diagnosis of the disease [3,12].

The pathogenesis of this pain is linked to SFN [21].

SFN is caused by damage of peripheral nerves including those myelinated (Aδ fibers) and those unmyelinated (unmyelinated C fibers). In SFN both somatic and autonomic fibers can be affected [22]. These fibers are responsible of converting temperature and pain sensation after stimulation of the skin. The main characteristic of SFN is the chronicity of the pain and the association with autonomic manifestations leading to decreased, absent or increased sweat, lachrymal and salivary production, and internal-organ smooth muscle involvement resulting in chronic diarrhea or constipation and blood pressure variations [23].

Unfortunately, often in FD patients ERT does not result in successful resolution of the SFN symptoms, neither alone or in association with typical pain treatments such as antiepileptics, antidepressant or opioids, that have also several side effects, including addiction [10–19]. The reason of incomplete response to ERT could be the presence of irreversible nerve damage. Poor data are available on the effect on pain of the available chaperone migalastat. New disease specific treatments such as gene therapy and the chaperone lucerastat are currently under clinical trials, the latter includes the effect on neuropathic pain as the primary end-point (MODIFY study: ClincalTrials.gov Identifier: NCT03425539). However, the management of pain in FD is challenging and requires a multimodal approach [18,19].

A role of the endocannabinoid system in the pathophysiology of the SFN has recently been demonstrated [24]. This system is involved in several mechanisms including neuromodulation at peripheral, spinal and supraspinal levels [25].

Indeed, the endocannabinoids receptors, which recognize three types of cannabinoids molecules, the synthetical compounds, endogenous endocannabinoids and the phytocannabinoids generated from the cannabis plant [25] are present in neurons throughout the nervous system and modulate the nociceptive transmission resulting in regulation of pain [22].

Recently, the use of cannabinoids has been proposed in alternative to standard therapies, for the treatment of unresponsive neuropathic pain in several disorders such as diabetes and multiple sclerosis [26].

The pharmacologically active components of cannabinoids include THC and CBD, which work together synergistically as agonists on the endocannabinoid system. The presence of CBD may improve the tolerability of the psychoactive side effects of THC [27].

Based on these evidences, we treated our patient with a balanced formulation containing both THC and CBD, which was well tolerated, without psychoactive side effects. The decision to start treatment was shared with the patient, after providing detailed information on possible risks and benefits. Interestingly the main positive result was obtained on nocturnal pain, allowing the patient to sleep again all night long, while the effect was less evident during the day. This could be explained by the additional effect of cannabinoids in improving sleep quality [28]. Of note, these positive results were maintained after one year of treatment. Unfortunately, cannabinoids had no effect on acute pain episodes that were still triggered by stress, exercise or changes in ambient temperature, indeed the score about “worst pain” at the BPI was unmodified. This kind of pain interfered with normal life activities intermittently,

this explain the different values at the item "enjoyment of life" of the BPI overtime.

In conclusion: although more evidence is needed, this case report suggests that the use of medical cannabis could be considered as a pain treatment option for patient with FD, in particular for nocturnal pain relief, when other pharmacological approaches have failed.

A clinical trial, including more patients, is needed to establish efficacy and safety of this analgesic approach in patients with FD and neuropathic pain.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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