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Medical Cannabinoids as Treatment for Hypophosphatasia-Related Symptoms

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Introduction

Hypophosphatasia (HPP) is a rare congenital metabolic multisystem disease characterized by low serum alkaline phosphatase levels. It is caused by a mutation of the gene encoding TNSALP (tissue nonspecific alkaline phosphatase) formation, an enzyme involved in phosphate metabolism [1, 2]. Low TNSALP activity results in accumulation of different metabolic products, such as phosphoethanolamine, pyridoxal phosphate, and inorganic pyrophosphate [2–4]. Clinical expressions can be multifaceted correspondingly. These can be described as a mixture of multilayered symptoms. Bone mineralization disorders, impaired skeletal growth, bone fractures, chondrocalcinosis of large joints, periarticular ossifications, and impaired tooth development are among the main phenotypic features [2–4].

Persistent muscle pain (whole body pain) as cardinal symptom arises from high concentration of inorganic pyrophosphate [1, 2]. High concentrations of pro-inflammatory cytokines trigger inflammatory reactions, autoimmune processes, and hyperprostaglandinism [5, 6]. Adenosine triphosphate-dependent energy transfer in muscle is therefore disrupted. Bone and joint pain occur due to the development of chondrocalcinosis via deposits of calcium pyrophosphate crystals [1, 2]. Pyrophosphate deposits are accompanied by pseudogout attacks along with periarthropathic calcifications [2].

Neurological pathologies due to cerebral metabolic disorders may be involved, such as headaches, pseudomeningism, and vitamin B6-dependent seizures [1–3, 7, 8]. Psychological/psychosomatic alterations such as anxiety, lack of drive, loss of motivation, and depressive episodes may occur. Nephrocalcinosis, progressive renal insufficiency, and gallstone disease are additional common effects [1, 2]. There are dominant and recessive forms of the disease which result in differing degrees of TNSALP impairment [9, 10]. Severe HPP has an early onset and affects an estimated 1:100,000–1:900,000 people [8, 11, 12]. Milder HPP cases exhibit fewer specific symptoms and may be as common as 1:2,500–1:6,370 [8, 13, 14].

Case Presentation

The patient is a female in her sixties from Germany of Central European ethnicity (157 cm, 92 kg). Main diagnosis is HPP (phenotype: infantile form, with high bone mass) as a multisystem disease with decreased muscle strength, scoliosis, facet joint syndrome, chronic recurrent lumbar back pain, and chronic pain syndrome.

Secondary diagnoses are Hashimoto thyroiditis, bronchial asthma, morphea, nephrolithiasis, cholecystolithiasis, obesity, and vitamin D deficiency. Current medication: asfotase alfa 80 mg three times weekly s.c., L-thyroxine 125 μg per day, budesonide/formoterol 160/4.5 μg twice daily by inhalation, vitamin D 1,000 IE per day, and cannabis extract (tetrahydrocannabinol [THC] 5 mg/mL/cannabidiol [CBD] 20 mg/mL) 2–3 × 0.5 mL per day (stably adjusted, slowly up-titrated beginning March 2021).

The patient works as a general physician in her own medical practice. She expressed HPP-related symptoms from birth and was treated for postpartum respiratory failure as a premature newborn. Conspicuous at birth were an implied turricephalus and hip dysplasia. Later, she largely skipped the crawling phase, using an unusual motor development of sliding across the floor.

Growing up, she suffered from tetanic seizures, likely due to impaired calcium metabolism. Other symptoms were periods of leg pain, muscle weakness, episodic occurrences of insatiable vomiting, frequent abdominal pain, recurrent pneumonia, increased dental caries and tooth loss, anxiety, syncopal seizures, and multiple bone fractures (clavicle, coccyx, mandible, carpal bones, metacarpal bones, kneecaps, and ribs). In adulthood, from 30 years onward, life-threatening laryngospasms occurred.

The patient makes it a point to mention that she was nevertheless able to climb trees, dance, and hike and had a happy childhood. Later, she achieved a university degree in medicine as a specialist in physical therapy and in general medicine. At the age of 23 years, she gave birth to one child. This was later followed by 4 miscarriages.

From childhood onward, the patient underwent numerous medical examinations in various specialties. However, it was not until 2008, at the age of 51 years, after a repeated (this time very severe) laryngospasm with oxygen deficiency and subsequent acute coronary syndrome, that the patient herself discovered her disease and had the diagnosis of HPP confirmed by genetic testing. Genetic testing (bone panel) shows an in-frame deletion of 6 amino acids in the c-terminus of the liver/bone/kidney alkaline phosphatase gene (ALPL): mut. ALPL c.1410_1427 and protein change p.Leu471_Glu476del.

Until then, she had received symptomatic treatments for seizures, pain, and muscle weakness. Therapeutic approaches included analgesia and seizure prophylaxis, as well as long-term physio-

therapy and psychotherapy. A causal therapy was administered starting in January 2019 and continued for the last 3 years with asfotase alfa 80 mg taken 3 times per week s.c. Enzyme replacement therapy resulted in an immediate resolution of the laryngospasms and a noticeable deceleration of further dental decay. However, lower lumbar, pelvic, and leg pain sensations and general muscle weakness increased in frequency and intensity and resulted in prolonged periods of work incapacity and repeated sick leaves.

Starting in November 2019, her symptoms worsened. Her pain was rated an 8 on average, with breakthrough pain up to 10/10 (NRS). During this period, her unaided walking distance decreased from an initial 50 m to 20 m.

Due to intolerability of her pain and the associated movement restrictions, her work was interrupted for 1 ½ years starting in 2019. This was possibly accompanied by post-COVID symptomatology and is interpreted as such by the patient in retrospect.

The patient received bridging neurosurgical and orthopedic interventions at the lumbar facet joints between 2017 and 2021. Various therapy attempts with different methods of physiotherapy were made over the patient's lifespan.

Before 2020, physical mobility was regularly augmented by swimming, water aerobics, and aqua cycling. She received long-term psychotherapy (both psychodynamic psychotherapy and behavioral therapy) over 10 years. Additionally, she practiced mindfulness meditation and autogenic training. Up until 2017, she had generally managed to maintain a good mood and a positive outlook on life. Beginning in 2017 and intensifying in November 2019, she began to suffer from increasingly intolerable pain attacks and regularly reported feelings of hopelessness and fears of not being able to cope with her situation and work. She never reported suicidality.

She received buprenorphine patches (5 μg/h) and piritramide 15 mg s.c. for breakthrough pain (0–2 times per week). Higher doses of opioids were not tolerated due to adverse gastrointestinal side effects (severe nausea and severe obstipation). She received regular therapeutic injections of local anesthetics and corticosteroids for the sacroiliac and facet joints over a 4-year period (estimated average: once every 8 weeks). Facet joint denervation at the lumbar spine was performed in 2017 and 2020 but did not provide lasting relief. For current mobility, she uses a rollator or crutches, cervical and lumbar supports, knee braces, and a grasping aid. Nonsteroidal anti-inflammatory drugs were not administered due to type 1 allergic reactions to ibuprofen, diclofenac, etoricoxib, and aminophenazone. No further substances of that class were tried after an anaphylactic reaction to metamizole. Methocarbamol was not found to be effective.

Cannabinoid therapy was started with a full-spectrum cannabis extract (THC 25 mg/mL/CBD 5 mg/mL) 0.05 mL 2 times per day and gradually increased to 0.15 mL 2–3 times per day. This reduced the average pain but also produced several side effects: nausea, lack of drive, difficulty concentrating, and a feeling of detachment. The preparation was adjusted to THC 5 mg/mL/CBD 20 mg/mL 0.1 mL 3 times per day and then gradually increased to 0.5 mL 2–3 times per day, corresponding to 10 mg of CBD and 2.5 mg of THC 2–3 times per day.

The cannabinoid regimen was well tolerated. The only side effect was slight temporary drowsiness. Average pain decreased to 2–3/10 NRS and has remained at this level to date. The patient also reported a reduction of anxiety from 8–10/10 to 1–3/10 NRS and a significant improvement of sleep quality and current quality of life. Her mobility increased due to optimized pain control. However, muscular weakness persists, and unaided walking distance remains limited to 20 m. As of April 2022, she has successfully resumed working part-time in her family practice for the last 2 months.

Conclusion

In this case, medical cannabinoid therapy resulted in clinically significant improvement where several other therapies had been ineffective. The significant effect is particularly noteworthy considering the variety of therapeutic approaches previously tried (pharmacological, psychological, physiotherapeutic, etc.). For this reason, cannabinoids are presented as a possible independent treatment option for HPP-related pain.

Also worth noting is the positive response of HPP-related pain to a CBD-dominant full-spectrum cannabis extract, which the patient received only after being prescribed a THC-dominant cannabinoid extract which was not tolerated due to side effects. It is known that CBD can improve the tolerance of THC. CBD causes an allosteric modulation at the CB1 receptor so that THC effects mediated through it, including paradoxical nausea, are attenuated [15]. This may have been the case here as well. This also shows how the effects of cannabinoid-containing drugs can vary depending on their active ingredient composition. This suggests that in clinical practice, if a cannabinoid treatment is not responding, a different cannabinoid compound preparation can be tried.

THC and CBD have known anti-inflammatory properties that have been demonstrated both through in vitro models and in vivo [16–21]. Therapy of HPP-related pain commonly involves nonsteroidal anti-inflammatory drugs [5, 22–24]. In this case, these could not be administered due to allergic sensitization. Known cyclooxygenase-2 inhibition (COX-2 inhibition) of THC and CBD might explain the particularly good response to a full-spectrum cannabis extract in this case [25, 26]. Considering known side effects of long-term NSAID therapy (especially cardiovascular and gastrointestinal complications) [27–30], cannabis extracts may pose valuable additional therapeutic options for treating chronic HPP-related pain based on the potential anti-inflammatory effect or other scientifically unexplored effects of THC and CBD on HPP-specific pathways.

Adverse effects of cannabis medicines, adverse psychoactive reactions, and the development of substance tolerance are primarily related to THC [31]. CBD-predominant chemovars with a lower THC content tend to be better tolerated and seem to provide an optimized symptom control [31]. In comparison to THC, CBD is less potent in equivalent dosages. Therefore, cannabinoid therapies may require much higher CBD doses to effectively attenuate unwanted psychoactivity or adverse cardiovascular events, such as THC-associated tachycardia, and to induce intended reductions in pain and inflammation [31]. Generally, cannabinoid dosing should start at modest amounts, and titration of cannabis preparations should preferably be done slowly over a period of up to 2 weeks.

Another interesting aspect is the so-called essential oils, called terpenes or terpenoids, that are produced by the cannabis plant and to which the cannabinoids THC and CBD belong. Over 100 of them are found in the *Cannabis sativa* plant. Most abundant terpenes include limonene, α-myrcene, α-pinene, β-caryophyllene, linalool, humulene, nerolidol, terpinolene, and ocimene. Unfortunately, the manufacturer of the full-spectrum cannabinoid does not provide a breakdown of the terpene profile, even upon explicit request in the context of this case report. There is a considerable amount of preliminary scientific evidence showing that many of the terpenes found in cannabis exert biological effects. Several of them, such as β-caryophyllene, α-myrcene, and limonene, have been shown to have antioxidant properties [32]. Others, including α-pinene, α-myrcene, and β-caryophyllene, have anti-inflammatory effects, for example, in the case of β-caryophyllene, by acting as agonists at the CB2 receptor [15]. Furthermore, anxiolytic and antidepressant properties of β-caryophyllene have been described [33, 34]. Presumably, terpenes play a greater role in inhaled use of cannabis than in oral use, an area of research that deserves more attention. While the oral route of cannabinoid administration in this patient may mean the terpenes play only a minor role in this case, more research may shed light on possible or potential effects.

The generalizability of this case is limited. However, because of the rarity of HPP, the observations are valuable. This patient suffers from a complex chronic pain syndrome. The factors involved in her multifaceted HPP disease course and how they interact are unknown, which is not uncommon in clinical practice.

Cannabinoids already have an increasing role in the treatment of chronic pain [35–39]. However, access to medical cannabinoids is particularly limited in many countries [39–41]. Legal restrictions for cannabinoids often far exceed those for opioids [42]. This is largely embedded in an ideological historic debate about societal risks and benefits of cannabis. One consequence of limited access to medical cannabinoids is the low prevalence of qualified prescribing physicians [39, 43–45]. In the light of our patient's lifelong medical trajectory and her current stable improvement under cannabinoids, we suggest further scientific evaluation of cannabinoids as treatment for HPP. In general, we propose more widespread information and training regarding cannabinoid therapies among physicians involved in or prescribing pain management. Clinical research on the potential usefulness of cannabinoids in rare diseases like HPP is also warranted. Also, health economic evaluations of cannabinoid therapy for chronic pain should be encouraged.

The Patient's Perspective

"I feel very grateful that I started therapy with cannabinoid medicine because during the course of my genetic condition of hypophosphatasia, I had developed unbearable pain.

Within the first few weeks of taking the drug, I was able to sleep through the night again without tossing and turning all night in excruciating pain. My life changed fundamentally as a result of cannabis therapy. I was finally able to rest again. Even if at times, very rarely, there are still occasional intense sensations of pain, the therapy helps me to recover more quickly from the situation.

About half a year after the start of the therapy, I was able to resume my work gradually, step by step. This was a major moment for me to have regained an important part of my life again. That is overwhelmingly wonderful and makes life much more interesting and worth living again."

Acknowledgment

Special thanks to the patient who remains anonymous.

Statement of Ethics

This case report has been created in accordance with the Declaration of Helsinki in its currently valid version, the guidelines of the International Conference on Harmonization of Good Clinical Practice, and the applicable German laws. The patient gave her written informed consent to the publication of this case report on March 5, 2022.

Conflict of Interest Statement

C.K. regularly prescribes cannabinoid-containing medications in his clinical activities and performs clinical research on cannabinoids. There are no links to specific manufacturers in terms of his prescribing practices. No further conflicts of interest were declared.

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Author Contributions

Conceptualization and investigation: J.M.F. and C.K.; writing – initial draft: J.M.F. and M.J.; writing – review and editing: all authors; supervision: J.M.F. and C.K.; and all authors read and approved the final manuscript.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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