Primary Periodic Paralysis

MORBIDITY AND IMPACT ON QUALITY OF LIFE

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INTRODUCTION

An Expert Roundtable on Primary Periodic Paralysis (PPP) was sponsored by Strongbridge in January 2019. The meeting brought together a group of expert clinicians and researchers specializing in neuromuscular disorders, representing a variety of academic institutions and teaching hospitals across the nation. Objectives of the Expert Roundtable were to discuss the current state of knowledge about PPP and to identify unmet needs in the diagnostic journey of patients with these conditions. With the goal of raising awareness of clinical challenges and best practices related to PPP, the authors present a 3-part series of white papers focusing on different aspects of PPP. This second paper explores the morbidity of PPP and the impact of the disease on patients' quality of life (QoL).

> These syndromes are so rare, and their presentation so variable, that many patients have difficulty receiving an accurate diagnosis. Some may have normal electrolytes at the time of diagnosis, but still be diagnosed with PPP. A negative genetic test also does not entirely exclude a diagnosis of PPP. Some patients have reported being suspected of malingering, which, in my experience, can greatly exacerbate the patient's suffering..
>
> **—Jeffrey Rosenfeld, MD, PhD, FAAN, FANA**

OVERVIEW OF DISEASE CHARACTERISTICS

PPP is a group of rare genetic neuromuscular disorders caused by mutations in skeletal muscle sodium, calcium, and potassium genes.[1,2] The disorders are clinically characterized by recurrent attacks of temporary flaccid muscle weakness that recover spontaneously.[3] Attacks may occur in response to specific triggers (diet, stress, or rest after exercise) or occur spontaneously.[1] In addition, these attacks may last from an hour to a few days, and they occur at irregular intervals.[4] Patients with hyperkalemic periodic paralysis (hyperPP), including those with paramyotonia congenita (PMC), may experience muscle stiffness between episodes of weakness.[5] Distinguishing clinical features of types of PPP were presented in the first paper in this series, but a common feature is their rarity. The prevalences of the subtypes of periodic paralyses are estimated to be hypokalemic periodic paralysis (hypoPP) 1/100,000,[6] hyperPP 1/200,000,[7] PMC 1/250,000,[7] and Andersen-Tawil syndrome (ATS) 1/1,000,000.[7]

As patients get older, the manifestations of PPP may change, as revealed by a survey in 66 patients between 41 and 82 years old with PPP. The majority—64%—experienced an unchanged frequency of attacks. In 21%, the frequency of attacks decreased, and 11% had attacks that were more frequent. Four percent of the patients were unsure if their attack frequency had increased or decreased.[8] In an effort to reduce the frequency of attacks, respondents in this study noted they employed strategies such as pacing activity level and the use of appliances to reduce ph ysical effort, avoiding repetitive or unnecessary movement, and resting when needed.[8] Some patients with PPP had given up activities they enjoyed, including gardening and visiting friends, or experienced difficulty performing daily tasks like blow-drying their hair and addressing personal hygiene.[9]

The severity of PPP attacks also varied among patients. Whereas 58% of patients said they experienced unchanged severity, 30% reported decreased severity as they aged, and 6% were unsure.[8] Nearly two-thirds of respondents (mean age, 60 +/- 14 years) said that they had PMW. As many as 23% were unsure if their weakness was permanent, and 9% did not experience PMW at all.[8]

> An early sign of permanent muscle weakness (PMW) is difficulty getting out of a chair, requiring patients to use their arms to push up from a seated position.
>
> **— John C. Kincaid, MD, FAAN**

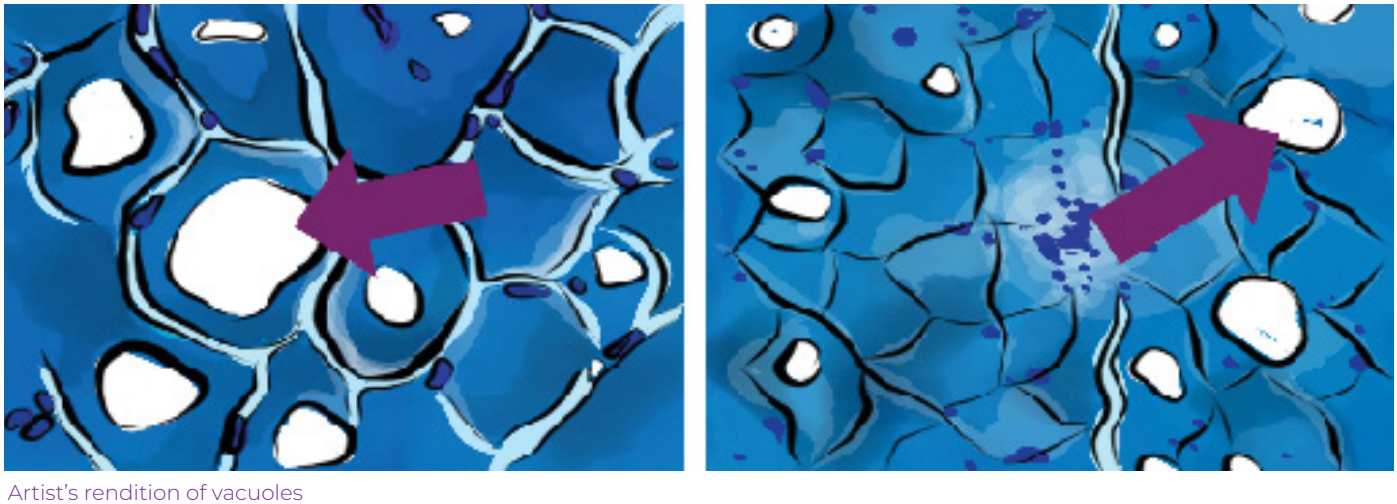
A CLOSER LOOK AT PERMANENT MUSCLE WEAKNESS

Over time, progressive, fixed weakness due to replacement of muscle by fibrous tissue and fat, can develop in some patients.[8,10] Diagnostically referred to as PMW, it typically involves a decrease in strength in the proximal lower extremities, and can vary in severity, as demonstrated in a study that involved 11 cases from a family with PPP, including case histories, radiography, serum studies, electromyography, muscle biopsy, and survey autopsy in 2 patients.[11] PMW is defined as muscle weakness that is always present and varies little from day to day.[8] One survey found that PMW is observed in up to 60% of patients in their fifties and sixties. However, patients may not be aware of their condition, and it can go undiagnosed.[8] As demonstrated in a survey by Cavel-Greant, about a quarter of patients with PMW eventually need assistance to walk and almost half require a mobility aid such as a wheelchair.[8] In the same survey of patients with PMW, 82% complained of muscle pain, and 43% of those rated the pain as moderate to severe in intensity.[8] Some physicians have delayed treating attacks of episodic weakness in PPP due to the opinion that these attacks stop after age 40, even though it has been suggested that continuous treatment may delay fatty muscle replacement.[8] The etiology of late-onset PMW is still unknown.[8] However, the

> While the association between PPP attack severity and/or frequency with development of permanent muscle weakness is unclear, anecdotal evidence has reported improvement in fixed muscle weakness with therapy.
>
> **—Mohammad Salajegheh, MD**

ictal pathophysiologic correlates of PPP may suggest a possible mechanism. Skeletal muscle biopsy samples show large distinctive central vacuoles[5,10] (in hyperPP and hypoPP, but not ATS–**Figure 1**),[7,13] variability in fiber size,[6] rounded fibers,[6,10] central nuclei,[6] and tubular aggregates.[6,7] One study that performed electron microscopy on a biopsy sample from a patient with hyperPP also showed myofibrillary disorganization and granular degeneration.[14] These findings occur in both weak and clinically normal muscles, but the number of atrophic fibers is proportional to the severity of muscle weakness.[13] These histological findings can be observed[5] in hypoPP and hyperPP.[14] Some abnormalities, such as vacuoles and necrotic fibers, are only detectible during an attack, and may not provide a definitive diagnosis.[7,13]

Figure 1. Vacuoles Typically Found on Biopsy in HypoPP



Artist's rendition of vacuoles

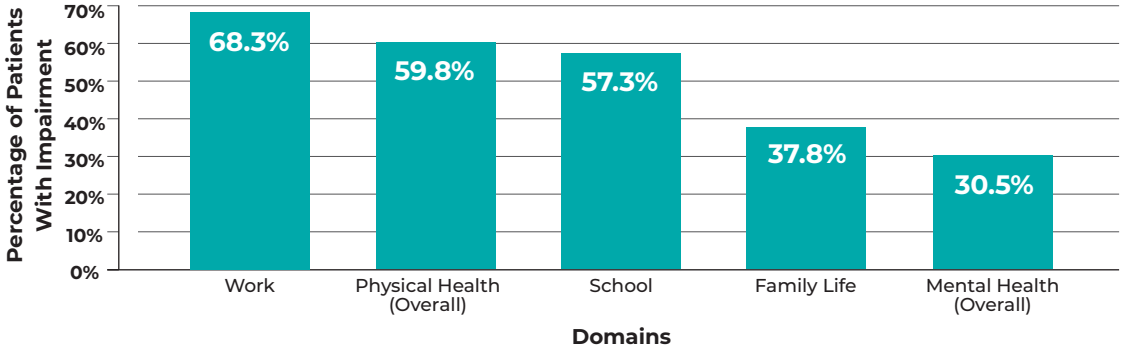
THE IMPACT OF PPP AND PMW ON PATIENTS' LIVES

Although PPP is rare, variable among patients, and often difficult to diagnose, its impact on patients' lives is considerable, including in later years when PMW can develop. As reported by the Cavel-Greant survey with patients over 41 years of age, the disease leads to loss of function in many aspects of life. As many as 92% of patients report reduced strength or stamina, 89% have difficulty with activities of daily living, 75% cannot tolerate mild exercise, 55% experience a lack of endurance, and 25% need assistance to walk only a few steps.[8]

Not surprisingly, considering the physical impact of PPP, patients experience impairment across multiple domains: 68.3% have difficulties with work, 59.8% see effects on overall physical health, 57.3% have difficulties with school, 37.8% experience challenges in their family life, and 30.5% are impaired in their overall mental health.[5]

Other features of PPP, especially when PMW has developed, include pain (82%), fatigue (89%), and injury from falls severe enough to require medical attention (67%), which included bruises, sprains, torn ligaments and joint capsules, cartilage damage, bone fractures, concussion, and internal bleeding.[8] Nearly half of patients were forced to use a mobility aid.[8] About a third also experienced depression.[8]

Channelopathies like PPP are often considered "benign" disorders because weakness is experienced episodically, and the heart and lungs are usually not impacted. Due to the rareness of these disorders and the idea that they are benign, there have been limited studies on the impact of muscle symptoms on patients' perceptions of QoL.[12] One study systematically evaluated the impact of skeletal muscle symptoms on QoL in individuals with skeletal muscle channelopathies. Participants included 16 people with hypoPP, 10 people with hyperPP, 4 people with ATS, and 36 people with autosomal recessive myotonia congenita.[12] The control group consisted of 422 age- and disease duration-matched patients with myotonic dystrophy types 1 and 2.[12] In addition to the Short Form Health Survey-36 (SF-36), a commonly used general measure of QoL, Sansone and colleagues utilized the Individualized Neuromuscular Quality of Life (INQoL) scale. This scale was designed specifically for use in neuromuscular disorders and measures of impairment across multiple domains, including weakness, myotonia, pain, fatigue, activities, independence, social relationships, emotions, body image, and treatment effects and expectations.[9] Multiple domains of the SF-36 showed statistically significant impairment in patients with PPP compared with the control group ($P<0.05$), including physical function, general health, vitality, and role limitations due to emotional problems.[12] On the INQoL, patients with PPP had impairments related to myotonia, pain, fatigue, activities, and emotions. Sansone and colleagues demonstrated that, overall, the QoL impairment on the INQoL associated with PPP was similar to myotonic dystrophy types 1 and 2.[12]



Many patients accommodate their activities and avoid doing things that may provoke attacks.

—Carlayne E. Jackson, MD

SUMMARY

PPP comprises a group of rare, progressive diseases that affect muscle resulting in acute attacks of muscle weakness and paralysis. These disorders can have a profound impact on QoL and ability to perform activities of daily living. Both physical and psychological domains are affected, with many patients reporting depression and anxiety related to fear of having their next attack. The frequency and severity of acute attacks varies from patient to patient. Moreover, a majority of patients with PPP will develop PMW as they age. Development of PMW severity varies among patients, and causes further impact on patients' mobility and quality of life.[8] These disorders impact multiple domains of QoL and can produce impairment comparable to some of the muscular dystrophies.

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