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Perspective

The Role of the Patient Partnership in Designing Research on Neuropsychiatric Issues in Hypoparathyroidism

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Abstract

Hypoparathyroidism is a rare endocrine disease that is associated with hypocalcemia and insufficient parathyroid hormone (PTH) levels. Neuropsychiatric complaints are common in hypoparathyroidism. Yet there is a large knowledge gap in our understanding of cognitive dysfunction in hypoparathyroidism and partnering with patients is essential for filling this hole. Input from hypoparathyroid patients is needed to define objective, performance-based cognitive impairments. Creating patient advisory boards that provide input for planning clinical trials would enable patient perspectives to be shared. This would ensure that meaningful, standardized neuropsychological instruments that prioritize patients' cognitive concerns are selected. Patient partnership is also needed to understand the wide inter-individual variability of cognitive symptoms in hypoparathyroidism, as well as mechanisms aside from calcium shifts that might explain cognitive symptoms, such as low PTH itself, alterations in brain structure, or other hypoparathyroidism-associated comorbidities. With new PTH replacement therapies on the horizon, patient input about studying how these therapies impact, and maybe even reverse, cognitive impairment will also be critical. Ultimately, the inclusion of patient partners in hypoparathyroidism research will advance the design of neuropsychiatric studies and generate key input for understanding how to reduce the burden of this disease.

Key Words: hypoparathyroidism, neuropsychiatric, cognition, partnership

Abbreviations: PTH, parathyroid hormone; SF-36, 36-item Short Form Health Survey.

Hypoparathyroidism is a rare endocrine disease that is associated with hypocalcemia and insufficient parathyroid hormone (PTH) levels. Hypoparathyroid individuals frequently suffer from symptoms that impair their daily function, despite conventional therapy with calcium and activated vitamin D. Symptoms include physical, emotional, and cognitive difficulties. Physical symptoms are typically paresthesias and muscle cramps, while emotional symptoms include depression and anxiety. Cognitive symptoms, often described by patients as "brain fog," include poor memory and slowed thinking. The constellation of these symptoms can have debilitating effects for people with hypoparathyroidism in their personal and professional lives. Yet there is a gap in our understanding of the neuropsychiatric issues that hypoparathyroid patients face. We lack information about the objective assessment and precipitants of cognitive symptoms, as well as the effects of PTH therapy and other management strategies to mitigate them. Partnering with hypoparathyroid patients, namely those who have the lived experience of these symptoms, is essential for designing research that will address patients' priorities in this area.

The physical, emotional, and cognitive symptoms of hypoparathyroidism are well-known. Physically, patients report fatigue, muscle twitching, spasms, and paresthesias, or in severe cases, seizures. For example, interviews with hypoparathyroid patients whose demographics were typical of the disease (mostly women with postsurgical hypoparathyroidism) revealed that more than 80% reported parasthesias, muscle cramping, and fatigue [1]. The emotional symptoms of hypoparathyroidism are similarly well-described. Depression is common; in a recent systematic review of PubMed, Embase, and Cochrane CENTRAL reports that included data on 18 973 hypoparathyroid patients, depression was present in 9% and ranked among the 9 most common complications of the disease [2]. Anxiety is also typical. In a survey known as the "Voices of Hypopara" [3] among 142 members of the Hypoparathyroidism Association, the largest US hypoparathyroidism advocacy group, most respondents (predominantly female and White) reported anxiety for multiple reasons. One was apprehension about the future, with fears about being able to take care of oneself and one's family and being able to continue to work. Other participants cited anxiety about the long-term consequences of the disease (alluding to tissue calcification and kidney damage). Disturbingly, respondents also felt anxious because their physicians did not understand their suffering and they had been repeatedly told by their doctors that "nothing was wrong." In addition to these physical and emotional symptoms, cognitive complaints are a common aspect of hypoparathyroidism, with a body of literature documenting poor quality of life. "Brain fog" is

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reported by approximately half of patients, with complaints of memory loss and difficulty with having a conversation and concentrating [1]. As one 49-year-old woman with postsurgical hypoparathyroidism poignantly explained, "I can't remember somebody's name that they just told me two seconds ago, and I can't remember my last thought" [1]. Tools such as the well-validated Short Form Health Survey (SF-36), which is a self-report of general quality of life, and more recent disease-specific instruments, have amply documented how these physical, emotional, and cognitive deficits can markedly compromise well-being, physical activity, functioning at home and at work, and inter-personal relationships.

Fortunately, PTH therapy appears to reverse these symptoms. In open-label studies with rhPTH(1-84) and PTH(1-34), quality-of-life symptoms as measured by the SF-36 improved, and in the registration trial of rhPTH(1-84), there was an improvement in the treatment group, particularly in those with the worst baseline scores, although the between-group difference was not significant [4], possibly due to differences between geographical subgroups. Recently, treatment with palopegteriparatide was shown to improve quality of life as compared to placebo using both the SF-36 and a disease-specific instrument [5].

Despite the strong relationship between PTH treatment and improvement in symptoms and quality of life in hypoparathyroid patients, there is still a large knowledge gap in our understanding of cognitive dysfunction in hypoparathyroidism. Partnering with our hypoparathyroid patients is essential in order to better define and quantify their cognitive dysfunction. It remains unclear what and how severe the objective cognitive deficits are in hypoparathyroidism. The hypoparathyroidism quality-of-life literature reflects participants' subjective self-perception of their lack of well-being. To define objective, performance-based cognitive impairments, input from hypoparathyroid patients is needed. Creating patient advisory boards that provide input for planning clinical trials would enable patient perspectives to be shared. Patient advisors could help select the standardized and validated psychometric tests of the cognitive domains that align with their concerns and priorities. Cognitive function encompasses multiple components, including but not limited to language, vocabulary, semantic fluency (generating words in different categories), executive function (cognitive flexibility), attention (focusing on relevant stimuli in the presence of irrelevant stimuli), episodic memory (remembering things experienced at particular times and places), working memory (remembering and seeing connections between items or ideas), semantic memory (long-term memory of general knowledge), visual memory (recalling visual information), auditory memory (recalling oral information), processing speed (quickly taking in and using information) and visuo-spatial functioning (comprehending physical relationships). Limited reports have documented impaired cognitive function in nonsurgical hypoparathyroid patients, including reduced inhibitory control or an inability to suppress a thought, action, or feeling or a lack of "self-control," impairment in visuo-spatial functioning, and psychomotor retardation [6]. In postsurgical hypoparathyroidism, the scant available data are variable, with one small study of predominantly White women showing impaired cognition, particularly slowed processing speed [7], and another report not finding a difference from controls but demonstrating that lower serum calcium levels were associated with worse visuo-spatial attention, executive function, and semantic memory scores [8]. Integrating hypoparathyroid patients' points of view is necessary to ascertain whether more studies are needed with formally administered cognitive testing by trained neuropsychologists. If so, input from patients would ensure that meaningful, standardized neuropsychological instruments that prioritize their cognitive concerns are selected.

Patient partnership is also needed to understand the wide inter-individual variability of cognitive symptoms in hypoparathyroidism. Some patients never experience "brain fog" and live highly functional lives, with participation in competitive sports and achievement of professional success, while others are severely debilitated and cannot stay in school, their job or adequately care for their children. It may be that differences in demographic characteristics contribute to this range of cognitive symptoms. Most hypoparathyroidism studies have comprised young or perimenopausal White, non-Hispanic women with postsurgical disease. Future studies could include patient advisory boards with diverse members, which might facilitate greater inclusion in studies of participants who are male, older, of other races and ethnicities, and have nonsurgical disease. This broader range of participants could lead to insights into the wide spectrum in the severity of cognitive complaints.

Patients with hypoparathyroidism have voiced their opinion regarding ways to reduce their risk of developing cognitive symptoms and severe episodes. They want to be able to know their calcium levels at the time of their symptoms and for their providers to acknowledge that they can be having symptoms despite "normal" blood calcium levels. Frequently, the symptoms occur in the context of a "calcium crash," a sudden drop in calcium levels that causes cognitive and physical symptoms. During such episodes, lower serum calcium levels likely decrease calcium influx to the cerebrospinal fluid and trigger cognitive dysfunction. Patients often live in fear of these episodes, with 84% citing extreme concern about them in the Voices of Hypopara survey [3]. Distressingly, these episodes can happen unexpectedly. Even more unsettling to patients is that they might be told that their calcium level is normal when they are symptomatic. This disconnect might occur because a random serum calcium level does not capture calcium fluctuation throughout the day. Partnering with patients has already shown that they view having immediate knowledge of their serum calcium level as a key approach to managing symptoms, with 99% of the Voices of Hypopara participants saying that they would use an at-home calcium monitoring device [3]. Access to information about real-time serum calcium levels, which can stave off a "crash," thus appears to be a patient priority for mitigating cognitive as well as physical symptoms.

Patient partnership is also needed to guide decision-making about studying mechanisms aside from calcium shifts that might elicit cognitive symptoms. Other hypoparathyroidism-related derangements, such as reduced PTH itself, might be causative. PTH crosses the blood brain barrier and interacts with central nervous system neurons expressing parathyroid hormone 2 receptor (PTH2R) in areas that are important for cognitive function. PTH also might influence regional cerebral capillary blood flow, such that reduced flow might alter neurovascular coupling. Input from patients about designing studies to dissect the contribution of PTH vs calcium on cognitive symptoms is necessary. Such studies could possibly involve separately perturbing calcium and PTH levels and looking at functional magnetic resonance imaging (fMRI)

and task-related changes in specific brain regions. Whether the volume of brain structures might be altered and whether such structural changes might correlate with cognitive impairment is also unknown. Understanding whether this knowledge would reduce the burden of disease and benefit the patient population would lead to shared decision making to guide research planning in this area.

Patient partners can also help to determine whether identifying causes external to hypoparathyroidism per se that might contribute to cognitive symptoms is a research priority. Hypo- and hyperthyroidism, frequent hypoparathyroidism comorbidities, are commonly associated with poor concentration and decreased memory. Input from patients is needed about the value of designing neuropsychiatric studies with careful attention to thyroid levels. Another possible contributor may be depression. This common diagnosis in hypoparathyroid patients might increase cognitive impairment. Integrating patients' preferences about whether this should be assessed as a possible confounder in future cognitive studies is needed, as well as the possible contributions of psychiatric or neurologically active medications. In addition, many hypoparathyroid patients are perimenopausal, a stage of life which is associated with forgetfulness, difficulties with word retrieval, and "brain fog." Careful consideration of patients' values about whether menstrual status and serum estradiol and FSH concentrations should be assessed in future studies will be needed. Finally, vascular risk factors such as high cholesterol levels (possibly in association with hypothyroidism), physical inactivity (possibly because of avoiding exercise-induced hypocalcemia), and vascular calcification (a complication of hypoparathyroidism) might contribute to diminished cerebral blood flow and vascular cognitive impairment. Guidance from patients can help to weigh the importance of including these variables in future cognitive studies.

Ultimately, the inclusion of patient partners in hypoparathyroidism research will advance the design of neuropsychiatric studies. Patients' preferences about studying potential approaches to benefit cognitive function, such as memory training, the use of external memory cues and organizational aids, as well as vascular risk factor optimization, should be explored. With new PTH replacement therapies on the horizon, patient input about studying how these impact, and maybe even reverse, cognitive impairment in controlled trials will also be critical. Including the patient perspective in designing hypoparathyroidism neuropsychiatric research will not only enhance patients' confidence that their medical and mental health providers as well as their family and friends recognize their suffering, but also generate invaluable input for understanding how to benefit the patients, the most vital stakeholders of clinical research, and reduce the burden of their disease.

Disclosures

Mishaela R. Rubin: research investigator for Takeda Pharmaceuticals; research investigator and advisor for Ascendis Pharmaceuticals.

Data Availability

No data were generated for this manuscript.

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