ABSTRACT

Objective: Hypoparathyroidism is a rare disease caused by lack of parathyroid hormone (PTH) leading to hypocalcemia, hyperphosphatemia, and a variety of symptoms. This study aimed to quantify the clinical and social burden of illness from the perspective of affected patients.

Methods: A web-based instrument was developed with input from patients, clinical experts, and the Hypoparathyroidism Association. Qualifying participants were ≥18 years old, diagnosed with hypoparathyroidism for ≥6 months, and U.S. residents. Questions focused on demographics, diagnosis perceptions, current attitudes, medical management, current symptoms, acute episodes, comorbidities, personal life, and employment.

Results: A total of 374 adults (mean age, 49 ± 12 years; female, 85%) with hypoparathyroidism (mean duration, 13 ± 12 years; severe condition, 30.5%) completed the survey. Patients reported visiting a mean of 6 ± 8 physicians before and after their diagnosis. The majority strongly agreed with feeling unprepared to manage the condition at diagnosis (56%), that controlling their hypoparathyroidism is harder than expected (60%), and that they were concerned about long-term complications of their current medications (75%). More than 10 symptoms were experienced by 72% of patients in the preceding 12 months, despite current management regimens. Symptoms were experienced for a mean of 13 ± 9 hours/day. Hospital stays or emergency department visits were required by 79% of patients. 45% reported significant interference with their lives, 85% reported an inability to perform household activities, and 20% experienced a disease-associated change in employment status.

Conclusion: Patients with hypoparathyroidism have a high burden of illness and experience a broad spectrum of symptoms, with a multidimensional impact on their lives.

INTRODUCTION

Hypoparathyroidism is a rare, complex endocrine disorder resulting from absent or inappropriately low levels of parathyroid hormone (PTH) (1-3). PTH is the principal regulator of serum calcium homeostasis (4). Deficiency of PTH results in a lack of control of mineral homeostasis involving calcium, phosphate, magnesium, and vitamin D levels. Hypoparathyroidism is characterized by hypocalcemia and often hyperphosphatemia (5). Patients experience significant short-term symptoms and long-term complications of both the disease and the currently available management regimens (6).

There is no PTH replacement treatment currently approved for patients with hypoparathyroidism. In fact, hypoparathyroidism is the last classic endocrine-deficiency disorder for which replacement therapy using the native hormone has not been approved by the U.S. Food and Drug Administration (7-9). The current standard of care for hypoparathyroidism is aimed at short-term symptom management, with large doses of oral calcium and active vitamin D (4,7,8). The high doses and sustained use of calcium
and active vitamin D warrant careful monitoring because long-term complications, such as soft-tissue calcifications, kidney stones, nephrocalcinosis, vitamin D intoxication (hypercalcemia and hypercalciuria), and renal failure, may occur (4, 7, 8, 10).

Reliable prevalence data for hypoparathyroidism are lacking, and reports of patient experiences with the condition are limited. In a review article summarizing presentations at the International Workshop on Hypoparathyroidism, Bilezikian et al reported that patients noted highly subjective and variable descriptions of disease-associated symptoms (6).

There is a need for more research to define the impact of the short- and long-term complications of this rare endocrine disorder. Mitchell et al reported biochemical and imaging findings from a review of patients with hypoparathyroidism identified from the Partners Healthcare System research patient data registry (11). Although the cohort maintained a goal low-normal serum calcium range, there were symptomatic episodes of both hypo- and hypercalcemia. A surprisingly high rate of renal and basal ganglia calcifications was also observed. Arlt et al conducted a small questionnaire-based study in females with postoperative hypoparathyroidism receiving stable calcium and vitamin D treatment compared with a control group of females after thyroid surgery who had intact parathyroid function (12). Females with hypoparathyroidism had clinically relevant impairment in mood and sense of well-being compared with the control group. As this impact on quality of life was present despite receiving the standard treatment option (stable calcium and vitamin D treatment), the authors noted it was conceivable that findings may be a direct result of PTH deficiency. Similarly, there is a lack of information about the unmet needs of this rare disease, including the burden of illness (4, 6, 8). This article reports the findings from the Patients’ Attitudes and Responses About Hypoparathyroidism Tolerance Explored (PARADOX) study. This was a comprehensive, cross-sectional patient survey that sought to quantify the burden of illness associated with hypoparathyroidism, with specific emphasis on the clinical and social burdens the condition imposes on patients.

**METHODS**

**Patients**

Eligible male and female patients were ≥18 years of age and U.S. residents. Hypoparathyroidism was diagnosed by a physician ≥6 months before study participation. Patients were excluded if their diagnosis was pseudohypoparathyroidism or pseudopseudohypoparathyroidism. Patients were eligible only if they reported, at screening, low levels of serum calcium or use of medication to manage low serum calcium levels. Eligible patients could be currently or previously enrolled in a clinical trial for the treatment of hypoparathyroidism.

**Study Design**

This was a web-based survey in which patients self-reported answers to an online nonvalidated questionnaire that was designed to take approximately 30 minutes to complete. Members of the Hypoparathyroidism Association, Inc., were invited to complete the survey and were asked to spread awareness of the study to nonmembers who have the condition. The Hypoparathyroidism Association, Inc. (www.hypopara.org) is a nonprofit organization that serves as a valuable worldwide resource for patients and treating physicians, offering a support network to almost 4,000 members and promoting public disease awareness. Social media forums were also used to recruit patients.

**Study Questionnaire and Analysis**

The study questions were developed with input from clinical experts, patients, the authors, and the Hypoparathyroidism Association. It was approved by the Institutional Review Board of the University of Mississippi. The questionnaire was divided into distinct topic areas of screening eligibility, demographics, diagnosis, and management; initial perceptions, current symptoms, perceptions, and therapy; acute episodes and comorbidities; and impact of disease on employment, personal and social life, and well-being. A 7-point Likert scale was used for the categories that determined management and perceptions; 1 equaled “strongly disagree” or “not at all satisfied” and 6 or 7 equaled “strongly agree” or “extremely satisfied.” Disease severity was self-reported by selecting mild, moderate, or severe. No definition or description of severity grades was provided on the questionnaire. Symptoms experienced in the last 12 months were selected from a list of 38 itemized symptoms organized into categories of physical (25 symptoms), cognitive (7), and emotional (6). Comorbidities were selected from a provided list of 6 medical conditions. Current medications were selected from a provided list of 11 therapies. Impact of disease was measured by determining level of interference on a 7-point Likert scale, on which 1 equaled “no interference” and 6 or 7 equaled “significant interference.” This interference scale was used for all questions about the patient’s ability to perform employment and household, personal, and social activities, as well as well-being. Other questions were multiple-choice selections or blank fields for the patient to complete using free text.

Once the online questionnaire was completed by a patient, it was checked to make sure the patient met the inclusion criteria. Questionnaires that did not match the patient inclusion criteria were excluded from the final data set. The data gathered from eligible patients were analyzed by overall population, sex, etiology (surgical or other), and disease severity (mild, moderate, or severe). Findings
presented here focus on the overall population and disease severity. The method of statistical analysis used for comparison of disease severity was the Student’s t-test with significance at the 95% confidence interval (CI) level.

RESULTS

The web-based survey was conducted between June 13 and July 23, 2012. The survey received 1,294 initial hits, 442 patients completed the screening portion, and 387 completed the questionnaire. The compliance check of completed questionnaires against the inclusion criteria resulted in 13 exclusions (all were patients with pseudohypoparathyroidism or pseudopseudohypoparathyroidism, not hypoparathyroidism). The final analyzed data set consisted of completed questionnaires from 374 patients. The demographics of these patients are provided in Table 1.

Healthcare Provider Interactions

A diagnosis of hypoparathyroidism was made by an endocrinologist for 51% of patients and by a surgeon for 25% of patients. The other patients reported being diagnosed by a primary care physician (general practitioner, family practitioner, or internal medicine physician, 15.8%); a neurologist, oncologist, or pediatrician (1.1% each); a pediatric endocrinologist (0.8%); or a gynecologist, nephrologist, or psychiatrist (0.3% each). A total of 2.7% couldn’t recall who made the diagnosis. Patients saw a mean of 6 ± 8 different physicians for evaluation of their symptoms before and after their diagnosis of hypoparathyroidism, with ≥60% of patients seeing ≥4 physicians.

The majority (98%) of patients reported currently having a healthcare provider treat and/or manage their hypoparathyroidism, with most managed by an endocrinologist (72%) or a primary care provider (21%). The other primary providers reported were nephrologists (2.7%), physician assistants (1.1%), oncologists or surgeons (0.5% each), and psychiatrists (0.3%). Patients reported seeing their managing physician for a mean of 4 ± 5 visits per year.

Patient Perceptions and Attitudes

At diagnosis, 56% of patients strongly agreed that they felt unprepared to manage their condition (Fig.1A). Although most (61%) patients felt that they were appropriately diagnosed, 48% strongly agreed with feeling mismanaged initially.

At the time of the survey, 60% of patients strongly agreed that controlling their hypoparathyroidism was harder than they expected, including concerns with their current medications (75%) (Fig. 1B). Seventy-nine percent of patients strongly agreed that most physicians do not understand hypoparathyroidism (Fig. 1B). Because of limited physician knowledge and experience with hypoparathyroidism, patients reported that they cycled through numerous physicians (mean ± SD, 6 ± 8) before selecting their primary healthcare provider to treat their hypoparathyroidism. Despite having cycled through multiple healthcare providers, 50% of patients were extremely satisfied with their current managing healthcare provider, and 11% were unsatisfied.

Medications

Table 2 lists the prescription and over-the-counter therapies that patients reported taking for management of hypoparathyroidism; 68% of patients were taking >1 medication, and 59% were taking >4 pills/day.

Calcium either alone or in combination with other agents (e.g., vitamin D) was used by 92% of patients.
Fig. 1. Perception and attitudes. Patients provided their perceptions and attitudes at diagnosis (A) and with current management (B). Responses were measured on a 7-point Likert scale.
Sixty-seven percent of patients reported a year-round burden of monitoring their calcium levels with ≥3 blood tests in the last 12-month period. Furthermore, 34% reported having ≥6 blood tests in that same period for their routine calcium level check.

**Ongoing Clinical Symptoms and Comorbidities**

Patients were asked to indicate which of 38 symptoms associated with hypoparathyroidism they experienced in the last 12 months despite taking current standard therapies. These symptoms were organized into 3 domains: physical (25 symptoms), cognitive (7), and emotional (6) (Fig. 2). Patients (n = 370) reported experiencing an average of 16 ± 8 of these symptoms, with 72% experiencing >10 symptoms. Patients with moderate or severe disease experienced a mean of 16 ± 7 and 19 ± 8 symptoms, respectively, compared with a mean of 9 ± 7 symptoms for patients with mild disease. Four patients did not report any symptoms; of these, 3 had mild disease and 1 was moderately affected. The survey included more females than males, as expected for this condition. Females were significantly more likely to report a greater number of symptoms than males (P<.05). On average, patients reported experiencing symptoms of hypoparathyroidism for 13 ± 9 hours/day. Disease severity was a contributing factor; patients with moderate and severe disease experienced symptoms 14 ± 8 and 16 ± 8 hours/day, respectively, whereas patients with mild disease experienced symptoms 6 ± 8 hours/day. In addition, patients with postsurgical hypoparathyroidism experienced symptoms for a longer duration during the day (mean ± SD, 13 ± 9 hours/day) compared with nonsurgical patients (11 ± 9 hours/day, P = .03).

**Physical Symptoms**

Figure 2 shows the complete list of 25 reported physical symptoms experienced in the last 12 months despite current medications. The physical symptoms reported by >50% of patients were fatigue (82%); muscle pain or cramping (78%); paresthesia (76%); tetany (70%); joint or bone pain (67%); and pain, heaviness, or weakness in extremities (53%). For each of these symptoms, the incidence was significantly higher in patients with moderate or severe disease than in patients with mild disease (fatigue, 88% and 86% vs. 61%, respectively; muscle pain or cramping, 80% and 88% vs. 59%; paresthesia, 81% [both] vs. 58%; tetany, 72% and 86% vs. 45%; joint or bone pain, 72% and 79% vs. 40%; pain, heaviness, or weakness in extremities, 53% and 70% vs. 26%; P<.05 for all). The incidence was significantly higher in patients with severe versus mild disease for the following complications: neuropathy (36% vs. 16%, respectively), edema (25% vs. 11%), respiratory problems (32.5% vs. 12.5%), nephrocalcinosis (22% vs. 6%), chronic kidney failure (19% vs. 2.5%), and soft-tissue calcifications (18% vs. 6%) (P<.05 for all).

**Cognitive Symptoms**

Figure 2 shows the complete list of 7 reported cognitive symptoms experienced in the last 12 months despite current medications. The cognitive symptoms reported by >50% of patients were mental lethargy (72%), inability to focus or concentrate (65%), memory loss or forgetfulness (61.5%), and sleep disturbances (57%).

**Emotional Symptoms**

Figure 2 shows the complete list of 6 reported emotional symptoms experienced in the last 12 months despite current medications. The emotional symptoms reported by >50% of patients were anxiety (59%) and depression (53%).

**Comorbidities and Acute Episodes**

Comorbidities were experienced by 259 patients (69%); the most frequently reported comorbidities were cardiac arrhythmias (66%) and kidney stones (35.5%).

<table>
<thead>
<tr>
<th>Medicationsa</th>
<th>Patients n (%) (n = 374)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination of calcium and active vitamin D</td>
<td>259 (66.6)</td>
</tr>
<tr>
<td>Active vitamin D capsules or liquid, oral (i.e., calcitriol)</td>
<td>165 (44.1)</td>
</tr>
<tr>
<td>Calcium tablets or chews, oral alone (i.e., calcium carbonate, calcium citrate)</td>
<td>94 (25.1)</td>
</tr>
<tr>
<td>Combination of calcium and magnesium (including antacids)</td>
<td>83 (22.2)</td>
</tr>
<tr>
<td>Vitamin D tablets, oral (i.e., ergocalciferol vitamin D$_2$ or cholecalciferol vitamin D$_3$)</td>
<td>74 (19.8)</td>
</tr>
<tr>
<td>Magnesium, oral</td>
<td>73 (19.5)</td>
</tr>
<tr>
<td>Parathyroid hormoneb</td>
<td>56 (15.0)</td>
</tr>
<tr>
<td>Muscle relaxers</td>
<td>31 (8.3)</td>
</tr>
<tr>
<td>Magnesium, topical</td>
<td>11 (2.9)</td>
</tr>
<tr>
<td>Phosphate binders</td>
<td>11 (2.9)</td>
</tr>
<tr>
<td>Teriparatide (i.e., Forteo®)c</td>
<td>10 (2.7)</td>
</tr>
<tr>
<td>No medication</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

a Listed by decreasing frequency of use.
b Any form of parathyroid hormone (PTH[1-34], PTH[1-84]) used by participants in clinical studies.
c Not approved by the U.S. Food & Drug Administration for this indication.
The hypoparathyroidism-associated symptoms and comorbidities translated to 79% of patients reporting hospital stays or emergency department visits due to their condition. The average number of reported lifetime visits to the emergency department was 6 ± 5. Patients with severe disease reported a lifetime average of 13 ± 24 emergency department visits, whereas patients with moderate and mild disease reported an average of 4 ± 8 and 2 ± 5.5 visits, respectively. The reported lifetime average number of days spent in the hospital that were attributed to hypoparathyroidism was 8 ± 16.5, with 44% spending 1 to 9 days and 19% spending >10 days. The length of stay correlated with disease severity; patients with severe disease stayed 14 ± 24 days, and patients with mild or moderate disease stayed 4 ± 9 and 6 ± 12 days, respectively. For both acute-episode settings, the annualized rate for patients with hypoparathyroidism exceeded the national average for the general population (emergency visits, 0.8 vs. 0.4; hospital days, 1.3 vs. 0.6, respectively) (13).

**Impact on Employment, Personal and Social life, and Well-being**

**Overall Quality of Life**

Patients (n = 374) were asked to consider all aspects of their condition over the preceding 12 months and to score how much hypoparathyroidism interfered with their life overall on a 7-point Likert scale. Significant interference (Likert score, 6-7) with life due to hypoparathyroidism was reported by 45% of patients. The impact of hypoparathyroidism on focused aspects of a patient’s life was assessed by surveying for the level of interference in their employment, personal and household tasks, social relationships, and well-being.

**Employment**

There was a decline in the number of patients with hypoparathyroidism reporting full- or part-time employment status over the course of their diagnosed lifetime (68% before diagnosis vs. 58% after; n = 374). More patients reported a current employment status of disabled (4.5% before diagnosis vs. 14% after, respectively), retired (6% vs. 10%), or unemployed (1% vs. 5%). Of the 18 patients who were currently unemployed, 72% attributed their status directly to their hypoparathyroidism. Overall, 20% of the 374 patients reported that conditions associated with their hypoparathyroidism (e.g., fatigue, inability to concentrate, or other symptoms) directly influenced their change in employment status. Of those patients, 44% reported a disabled employment status.

Hypoparathyroidism had a direct impact on work productivity for 78% of the 218 employed patients. These patients were absent 6 ± 14 days on average annually.
Furthermore, these patients reported an average of 65.5 ± 98 days during the last 12 months when they were present at work but were unable to perform at their full potential.

Activities and Relationships

Figure 3 presents the significant interference reported by patients on their ability to perform household and personal activities (Fig. 3A), on their social lives and relationships (Fig. 3B), and on their well-being (Fig. 3C). For 85% of the patients (n = 374), hypoparathyroidism prevented them from performing activities normally done around the house. A daily or weekly limitation in their ability to do these tasks was reported by 62% of patients. The majority of patients (72%) strongly agreed that it is difficult for family and friends to understand their condition.

DISCUSSION

Few publications have examined the clinical implications of hypoparathyroidism (2,11,12), and even fewer have examined the impact on the multiple facets of a patient’s personal and social life (2,12). The present study examined the burden of illness in 374 patients, which, to our knowledge, is the largest data set for patients with hypoparathyroidism to date. Most of the patients were members of the Hypoparathyroidism Association, Inc. (64%), reflecting the main distribution channel of the research questionnaire. The majority of the patients were female, similar to recent clinical trial demographics and consistent with the disease population (5,14). Analysis of the results by sex indicated that there was no statistical difference in the degree of disease severity by sex (data not shown).

Using this population-wide approach, the findings reveal a broad impact of hypoparathyroidism on a patient’s quality of life. Despite the current standard treatment...

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Self-reported Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidities</td>
<td>Last 12 Months n (%) (n = 138)</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>83 (60)</td>
</tr>
<tr>
<td>Kidney stones</td>
<td>36 (26)</td>
</tr>
<tr>
<td>Elevated bone mineral density</td>
<td>30 (22)</td>
</tr>
<tr>
<td>Decreased bone mineral density</td>
<td>24 (17)</td>
</tr>
<tr>
<td>Seizures or convulsions</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>7 (5)</td>
</tr>
</tbody>
</table>

\(^a\) Listed by decreasing frequency of occurrence

\(^b\) 31 patients ≥51 years of age

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Fig. 3. Impact of disease on everyday life. Patients reported significant interference with their ability to perform household and personal tasks (A), with social and personal relationships (B), and with their well-being (C). Responses were measured on a 7-point Likert scale; significant interference was rated as a 6 or 7. Percentages calculated from the number of patients who responded that tasks or relationships were applicable to them. Percentages provided for well-being are based on the total population (n = 374).
approach to symptoms using oral calcium, active vitamin D, and frequent serum calcium monitoring, patients with hypoparathyroidism experience a large burden of symptoms (physical, mental, and emotional) on a regular and persistent basis. Patients reported an average of 16 ± 8 symptoms over the last 12 months, and symptoms were experienced, on average, during 50% of the day. The symptoms experienced, especially the 6 most common physical (fatigue, muscle pain/cramping, paresthesia, tetany, joint or bone pain, pain/heaviness/weakness in extremities) and 4 most common cognitive (brain fog/mental lethargy, inability to focus/concentrate, memory loss/forgetfulness, sleep disturbances) symptoms, demonstrate the difficulty patients experience in performing daily functions because of the effects of hypoparathyroidism on muscles, bone, joints, extremities, and mental capabilities. Furthermore, symptoms manifest as fatigue (physical and mental), pain, paresthesia, tetany, memory loss, inability to concentrate, and overall discomfort.

The myriad physical complications and comorbidities experienced by the majority of patients emphasizes the long-term consequences and unmet need that remains despite current treatment options. The interference with employment encompassed both a reduction in employment status and a reduction in productivity for employed patients with hypoparathyroidism. A population-based study from Olmsted County, Minnesota, determined that the medical care costs for patients with hypoparathyroidism were almost 3 times those of the age- and sex-matched control group (15). Although this survey did not examine monetary burden, the data collected—including the demands that frequent acute episodes put on emergency departments and the need for hospitalization—suggest a heavy utilization of healthcare resources. These patient-reported data suggest that further exploration is needed to fully understand the complete burden on healthcare and insurance providers.

The burden of illness goes beyond clinical symptoms. The medication regimens and monitoring of serum calcium are time consuming. In most cases, multiple medications are required. For example, a combination of calcium and vitamin D was used by 67% of patients. The challenge to manage symptoms and clinical complications, despite treatment adherence, also includes routine checks of calcium levels. Thirty-four percent of patients reported taking ≥6 blood tests in a 12-month period just to check serum calcium levels. In addition, patients saw their managing physician 4 times/year.

Although the data clearly indicate that patients with hypoparathyroidism have a large burden of illness, there also appears to be a graded response based on disease severity. Patients with self-described moderate or severe hypoparathyroidism had almost twice the number of different clinical symptoms and significantly more occurrences of symptoms in the last 12 months compared with patients with mild disease. In addition to experiencing more symptoms, these patients also suffered from a nearly continuous daily presence of symptoms (14-16 hours/day). Beyond symptoms, the likelihood of clinical complications appeared to be associated with disease severity. Patients with severe disease had a significantly higher incidence of neuropathy, edema, respiratory problems, nephrocalcinosis, chronic kidney disease, and soft-tissue calcifications compared with patients with mild disease. The necessity of seeking care at emergency departments and lengthy hospital stays was doubled or tripled for patients with severe disease compared with patients with mild or moderate disease. Collectively, these itemized patient reports of symptoms, complications, and acute episodes serve to confirm the patients’ categorization of disease severity.

There are a number of limitations to this study. The self-reported nature of the survey did not allow for independent verification of the provided facts and experiences. It is possible that since the survey participants elected to become members of a support group, the Hypoparathyroidism Association, Inc., that their responses are reflective of a more symptomatic group than the general population of patients with hypoparathyroidism. The lack of an age- and sex-matched healthy control group precludes any comparisons to the general population. Finally, there was limited capture of monetary impact, preventing a health economics outcomes research model from determining the economic impact of hypoparathyroidism.

CONCLUSION

The extent of the negative impacts that hypoparathyroidism has on many facets of a typical adult’s health, well-being, and lifestyle, despite the use of the current standard of treatment, is perhaps the most striking result of this survey. The constant burden on patients’ overall well-being, coupled with patients’ perceptions of how poorly their healthcare provider understands their condition, suggests that an “empathy gap” exists. Patients have clearly expressed that their daily experience of this condition is not completely appreciated or understood by healthcare providers. These insights should be translated to disease education for healthcare providers that addresses the ongoing challenges involved in managing a rare condition through individualized symptom management. The research also points to the unmet medical need for new and effective treatment options. In addition, the study suggests that further research is needed to truly quantify the impact of hypoparathyroidism on health economic outcomes.

DISCLOSURE

Ms. Nandini Hadker and Ms. Jacqueline Egan have received a consulting fee from NPS Pharmaceuticals, Inc. Mr. James Sanders, President of Hypoparathyroidism Association, Inc., has no financial conflicts to disclose. Dr.
Hjalmar Lagast is an employee of NPS Pharmaceuticals, Inc. Dr. Bart L. Clarke is a consultant for NPS Pharmaceuticals, Inc. and has received institutional research grants and served as an advisory group member for NPS Pharmaceuticals, Inc.

REFERENCES