The impact of permanent muscle weakness on quality of life in periodic paralysis: a survey of 66 patients

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Abstract

Introduction

Patients with periodic paralysis (PP) have less muscle strength than normal. Their weakness is either episodic or permanent (1, 2). Episodic weakness consists of bouts of flaccid weakness with spontaneous remission which are distinguished by abnormal serum potassium levels during the bout (hyperkalaemic or hypokalaemic periodic paralysis, HyperPP or HypoPP). Permanent weakness includes an oedematous form which is reversible with treatment as well as irreversible forms (replacement of muscle by fibrous tissue and fat) (3). Permanent muscle weakness (PMW) is found in up to 60% of patients in their fifth and sixth decade (3) but is not always diagnosed because patients may be unaware of their handicap. Due to the generally accepted opinion that episodic weakness ceases after age 40, physicians may hesitate to administer treatment altogether even though it has been suggested that continuous treatment may delay the fatty muscle replacement (4). To document the challenges patients with periodic paralysis face as a result of PMW, we conducted a multinational online patient survey.

Patients, material and methods

Recruitment of participants

Survey participants were recruited by the support group Periodic Paralysis International (PPI) which maintains an e-mail service that informs patients of ongoing research activities worldwide. Survey participants were members of PPI and thus are a self-selected group of clinically diagnosed patients over the age of 40 years who sought support via the Internet. Patients willing to participate in survey research tend to be more motivated, often due to more severe illness. As such, findings may not necessarily be representative. The survey was hosted on the survey interface service Zoomerang (http://zoomerang.com) from 25th Nov 2011 to 3rd Jan 2012.

Survey contents

The survey contained 68 questions on age, gender, genetic diagnosis, clinical diagnosis, age at onset, age at diagnosis, medication history, episodic weakness, permanent weakness, additional muscle symptoms, incapacitation, injuries, mobility aids, compensation strategies, professional physiotherapy, and self-managed exercise.
Statistical analysis

Insofar as normally-distributed numerical values were obtained, means and standard deviations were calculated and, where applicable, populations were compared using Student's t-test. In some cases, median values with 95% confidence intervals were applied. For non-numerical values, the results were simply described using relative frequencies. All percentages were rounded to whole numbers.

Go to:

Results

Age and gender

Sixty-six patients aged between 41 and 82 years with a mean age of 60 ± 14 years participated in the survey. The gender was not totally evenly distributed as 30% were male and 70% were female. In the age group above 70 years (9 patients) there were no males.

Genetic and clinical diagnosis

A causative mutation was identified in 14 patients (24%). Seventy percent (70%) of participants were diagnosed as HypoPP, 9% as HyperPP, 6% as paramyotonia congenita (PC), 9% as Andersen syndrome (AS), and 6% were clinically diagnosed as periodic paralysis without specification of a subtype (excerpt of data in Table 1). Sixty-two percent (62%) had a known family history of PP, 24% were unsure of family history, 14% were sporadic cases. Family history was positive in 69% of patients with identified causative mutation and in 60% without an identified mutation and therefore did not influence success of genetic diagnosis.
Table 1.
Data excerpt: comparison of the diagnoses

| Causative mutations    | HypoPP (46) | HyperPP (6) | PC (4) | AS (6) | Unknown (4) |
|------------------------|-------------|-------------|--------|--------|-------------|
| Cav1.1-R528H           |             |             |        |        |             |
| Cav1.1-R1239H (4)      |             |             |        |        |             |
| Nav1.4-T704M           |             |             |        |        |             |
| Nav1.4-T1313M          |             |             |        |        |             |
| Kir2.1-R67W            |             |             |        |        |             |

Causative mutations

|                | percentage | percentage | percentage | percentage | percentage |
|----------------|-------------|-------------|------------|------------|------------|
| 28%            | 5%          | 25%         | 33%        | 0%         |

Mean current age

|                | 55 years | 49.5 years | 47 years | 46 years | 51 years |

Mean age at onset

|                | 16 years | 17.5 years | 2 years  | 17 years | 5.5 years |

Mean age at diagnosis

|                | 36 years | 34 years  | 33 years | 38 years | 46 years |

Mean disease duration

|                | 39 years | 32 years  | 45 years | 39 years | 45 years |

Positive family history

|                | 65%      | 17%       | 100%      | 83%       | 25%       |
| Causative mutations (absolute numbers) | HypoPP (46) | HyperPP (6) | PC (4) | AS (6) | Unknown (4) |
|--------------------------------------|-------------|-------------|--------|--------|-------------|
| Cav1.1-R528H (8)                     |             |             |        |        |             |
| Cav1.1-T704M (1)                     |             |             |        |        |             |
| Cav1.1-R1239H (4)                    |             |             |        |        |             |
| Cav1.1-R897S (1)                     |             |             |        |        |             |
| Nav1.4-T704M (1)                     |             |             |        |        |             |
| Nav1.4-T1313M (1)                    |             |             |        |        |             |
| Kir2.1-R67W (2)                      |             |             |        |        |             |
| Male                                 | 28%         | 50%         | 50%    | 33%    | 0%          |
| Female                               | 72%         | 50%         | 50%    | 67%    | 100%        |
| PMW                                  | 74%         | 50%         | 75%    | 83%    | 50%         |
| Current weekly episodes              | 20%         | 17%         | 50%    | 33%    | 25%         |
| Current daily episodes               | 41%         | 33%         | 50%    | 67%    | 50%         |
| Decreased frequency with age         | 17%         | 33%         | 25%    | 33%    | 25%         |
| Decreased severity with age          | 22%         | 50%         | 50%    | 33%    | 0%          |
| Causative mutations | HypoPP (46) | HyperPP (6) | PC (4) | AS (6) | Unknown (4) |
|---------------------|-------------|-------------|-------|--------|-------------|
| Cav1.1-R528H        |             |             |       |        |             |
| (8)                 |             |             |       |        |             |
| Nav1.4-T704M        |             |             |       |        |             |
| (1)                 |             |             |       |        |             |
| Nav1.4-T1313M       |             |             |       |        |             |
| Kir2.1-R67W         |             |             |       |        |             |
| Cav1.1-R1239H (4)   |             |             |       |        |             |
| Kir2.1-R897S        |             |             |       |        |             |
| (1)                 |             |             |       |        |             |

| Symptom             | HypoPP (46) | HyperPP (6) | PC (4) | AS (6) | Unknown (4) |
|---------------------|-------------|-------------|-------|--------|-------------|
| Pain                | 86%         | 67%         | 100%  | 100%   | 100%        |
| Fatigue             | 87%         | 83%         | 100%  | 100%   | 100%        |
| Stiffness           | 59%         | 83%         | 100%  | 67%    | 100%        |
| In youth moderately/very active | 89%       | 67%         | 75%   | 50%    | 100%        |
| In youth mildly active/sedentary  | 11%       | 33%         | 25%   | 50%    | 0%          |
| In age moderately/very active       | 13%       | 0%          | 50%   | 0%     | 25%         |
| Causative mutations    | Cav1.1-R528H | Nav1.4-T704M | Nav1.4-T1313M | Kir2.1-R67W | Unknown |
|------------------------|--------------|--------------|---------------|-------------|---------|
| (absolute numbers)     | (8)          | (1)          | (1)           | (2)         | -       |
| Cav1.1-R1239H (4)      |              |              |               |             |         |
| Cav1.1-R897S           | (1)          |              |               |             |         |
| In age mildly active/sedentary | 87% | 100% | 50% | 67% | 75% |
| Difficulty with daily activities | 87% | 83% | 100% | 100% | 100% |
| Difficulty with mild exercise | 98% | 100% | 75% | 100% | 100% |
| Injuries               | 33% | 50% | 50% | 33% | 25% |
| Mobility aids          | 48% | 17% | 25% | 67% | 67% |
| Benefit from physiotherapy | 50% | 50% | 0%  | 33% | 0% |
| Causative mutations (absolute numbers) | HypoPP (46) | HyperPP (6) | PC (4) | AS (6) | Unknown (4) |
|----------------------------------------|------------|-------------|-------|-------|-------------|
| Cav1.1-R528H (8)                       |            |             |       |       |             |
| Nav1.4-T704M (1)                       |            |             |       |       |             |
| Nav1.4-T1313M (1)                      |            |             |       |       |             |
| Kir2.1-R67W (2)                        |            |             |       |       |             |
| Cav1.1-R1239H (4)                      |            |             |       |       |             |
| Cav1.1-R897S (1)                       |            |             |       |       |             |

Deterioration from physiotherapy  
50% 50% 34% 67% 100%

Benefit from self-man. exercise  
66% 67% 34% 60% 33%

Deterioration f. self-man. exercise  
13% 0% 34% 40% 33%

Depression  
37% 17% 25% 33% 25%

**Age at onset and age at diagnosis**

Onset age was before 2 years in 14% and before 20 years in 74%. Only 15% had onset after the age of 30 years. Mean age of onset was 16.8 ± 13.8 years. Median age at which patients were diagnosed was 37.5 years. The mean latency between onset and diagnosis was 26 years. Age at diagnosis was bi-modally distributed with one peak during childhood and a second peak at approximately 40 years. Of the 17 patients diagnosed before age 20, 18% had no previously recognized family history, while 82% were from families with a recognized history of periodic paralysis, pointing to the importance of family awareness for early diagnosis (Fig. 1).
Figure 1.
Age at onset of symptoms and age at diagnosis.

The percentage of the 66 patients with age of onset (blue) and age of diagnosis (red) in each of the age groups (0-10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-82 years) is given. The yellow bar shows that the percentage of patients with onset at younger than 2 years makes up a fair portion of the age at onset group in the range of 0-10 years. Note the bi-modal distribution of the age at diagnosis and the latency between onset and diagnosis.

Episodic weakness

The frequency of episodes was weekly in 59%, daily in 28% and not present in 11%. With age, 21% of patients reported decreased frequency, 64% unchanged frequency, 11% increased frequency of weakness episodes while 4% were unsure (or the question did not apply, as they had only had PMW and no paralytic episodes). Likewise with age, 30% reported episodes of less severity, 58% of unchanged severity while 6% were unsure or the question did not apply. No patients reported increased severity of paralytic episodes.
Permanent weakness (PMW)

Sixty-eight percent (68%) reported muscle weakness which is always present and varies little from day-to-day, defined as PMW. Twenty-three percent (23%) were unsure if their weakness was permanent and 9% did not experience PMW. PMW was more prominent in proximal than in distal muscles (Fig. 2).

**Figure 2.**
Distribution of permanent muscle weakness.
For the subgroup of patients with permanent weakness (45 individuals), the percentage of patients with weakness in each muscle group is given. Note the frequency of weakness of the quadriceps muscle and hip girdle.

**Pain, fatigue, and muscle stiffness**
In the four weeks prior to the survey, 82% of participants reported experiencing pain, of these, 43% of moderate to severe intensity. Eighty-nine percent (89%) reported fatigue, of these,
66% of moderate to severe intensity. Sixty-seven percent (67%) reported muscle stiffness, of these 59% of moderate to severe intensity.

Incapacitation and injuries

At age 18-35 years, 83% were moderately to very active and 17% mildly active or sedentary; at the time of survey, 14% were moderately to very active and 86% mildly active or sedentary. Incapacitation was reported as follows: 92% had reduced strength and stamina, 89% reported difficulty performing activities of daily living, 89% felt limited in the type of work and activities they are able to do, 75% experienced difficulties with mild exercise, 55% report lack of endurance, 42% could climb only a single flight of stairs, 25% were unable to walk more than a few steps unaided. At the time of survey, 8% of patients reported they have as much strength and stamina as age-matched peers, but most of these individuals simultaneously reported PMW. Based on this, 91% are dissatisfied with what they were able to accomplish.

Sixty-seven percent (67%) reported injuries from falls which were severe enough to require medical attention. These included bruises, sprains, torn ligaments and joint capsules, injuries of cartilage, bone fractures, concussion, and internal bleeding.

Depression

Thirty-five percent (35%) of female patients and 33% of male patients reported depression, which three attributed to side effect from carbonic anhydrase inhibitor, specifically acetazolamide (Table 2). Patients expressed reluctance to discuss their depression with their physicians and may need reassurance that depression is often a consequence of chronic illness.
| Comparison of gender                                                                 | Male | Female |
|-------------------------------------------------------------------------------------|------|--------|
| portion of patients with permanent muscle weakness (PMW)                             | 65%  | 69%    |
| PMW in quadriceps (of portion of PMW patients)                                      | 70%  | 56%    |
| PMW in hip girdle (of portion of PMW patients)                                      | 40%  | 41%    |
| PMW in upper arms (of portion of PMW patients)                                      | 10%  | 41%    |
| PMW in calves (of portion of PMW patients)                                          | 20%  | 30%    |
| PMW in shoulder girdle (of portion of PMW patients)                                 | 10%  | 35%    |
| PMW in lower back (of portion of PMW patients)                                      | 15%  | 22%    |
| PMW in hands (of portion of PMW patients)                                           | 20%  | 20%    |
| PMW in neck/throat (of portion of PMW patients)                                     | 5%   | 26%    |
## Comparison of gender

|                           | Male | Female |
|---------------------------|------|--------|
| PMW in forearms (of portion of PMW patients) | 15%  | 20%    |
| PMW in gluts (of portion of PMW patients)    | 10%  | 20%    |
| PMW in trunk/chest (of portion of PMW patients) | 10%  | 15%    |
| PMW in face/jaws (of portion of PMW patients) | 5%   | 4%     |
| Current weekly episodes    | 15%  | 24%    |
| Current daily episodes     | 35%  | 35%    |
| Decreased frequency with age | 35%  | 15%    |
| Decreased severity with age | 35%  | 28%    |
| Pain                       | 58%  | 85%    |
| Fatigue                    | 85%  | 91%    |
| Category                                      | Male | Female |
|----------------------------------------------|------|--------|
| Stiffness                                    | 60%  | 70%    |
| In youth moderately/very active              | 90%  | 80%    |
| In youth mildly active/sedentary             | 10%  | 20%    |
| In age moderately/very active                | 20%  | 11%    |
| In age mildly active/sedentary               | 80%  | 89%    |
| Difficulty with daily activities             | 85%  | 91%    |
| Difficulty with mild exercise                | 15%  | 9%     |
| Benefit from physiotherapy                   | 55%  | 46%    |
| Deterioration from physiotherapy             | 18%  | 50%    |
| Benefit from self-man. exercise              | 50%  | 68%    |
Comparison of gender

|                          | Male | Female |
|--------------------------|------|--------|
| Deterioration from self-man. exercise | 28%  | 11%    |
| Depression               | 35%  | 33%    |

Mobility aids and compensation strategies

Forty-nine percent (49%) of patients use one or more mobility aids: 17% use a walker, 20% use a scooter, 23% use a wheelchair, 29% use a cane, 26% use other aids. In addition to mobility aids, patients employ a number of strategies to compensate for their handicap. These include: careful pacing of activity level and the use of appliances and devices to reduce physical effort, avoiding repetitive or unnecessary movement, resting when needed, using accessory muscle groups, and arranging or asking for help.

Professional physiotherapy versus self-managed exercise

Fifty-seven percent (57%) of participants have had professional physiotherapy. Of these, 49% experienced significant or mild benefit, 40% deterioration and 11% no change. Eighty-three percent (83%) of participants reported to have followed self-directed programs of exercise, of these, 62% experienced significant or mild benefit, 16% deterioration, and 22% no change (Fig. 3).
Figure 3.
Benefit of professional physiotherapy versus self-managed exercise.

Benefit from professional physiotherapy (in 38 patients) and self-managed exercise routines (55 patients). Note the large portion that deteriorated under profession physiotherapy. In contrast, note the large portion that benefited to different extents from the self-managed exercise.

The types of exercise differed little whether physiotherapy or self-directed, it was rather the intensity, frequency and duration of the sessions which differed. Patients who experienced increased weakness with physiotherapy made these representative comments; "Physiotherapist pushed me to use all my strength, work to the point of fatigue, accelerated the level of activity too quickly, and made me worse," "...triggered episodes of myotonia and made me worse," "I could manage at the start, but within a few weeks, I would get demonstrably weaker."

Subgroup analysis

To detect possible gender-specific effects, we performed subgroup analysis of males and females. There are tendencies for a differing distribution of muscle weakness, with males reporting more weakness in quadriceps muscles and females reporting more weakness of
arms, shoulder girdle and neck muscles. Also, females suffered more from pain, fatigue and stiffness than males and deteriorated more severely when undergoing physiotherapy (Table 2).

For examining the age-related development of weakness, patients were divided into three age groups: 41-50, 51-60, and 61-82 years. PMW was reported in 65%, 59% and 84% of patients, respectively, mainly due to weakness in quadriceps, hip girdle, and calves. There was a tendency for increased rates of PMW with age for almost all muscle groups except for muscles of trunk, face, and upper extremities which showed somewhat constant rates of PMW. Stiffness decreased in 81%, 68%, 50% of the patients in the respective age groups; whereas age did not affect pain, fatigue, or benefits from physiotherapy and self-managed exercise (Table 3).

Table 3.
Age-related development of weakness†.

| Age (years)   | 41-50 (n = 26) | 51-60 (n = 22) | 61-82 (n = 18) |
|--------------|----------------|----------------|----------------|
| PMW*‡ - overall | 65%            | 59%            | 84%            |
| PMW - quadriceps | 65%            | 59%            | 78%            |
| PMW - hip girdle  | 35%            | 45%            | 50%            |
| PMW - calves      | 19%            | 23%            | 50%            |
| Decreased stiffness | 81%         | 68%            | 50%            |

*PMW = permanent muscle weakness.
†Age did not affect pain, fatigue, or benefits from physiotherapy and self-managed exercise.
‡There was a tendency for increased rates of PMW for almost all muscle groups except for muscles of trunk, face, and upper extremities which showed somewhat constant rates of PMW.
Discussion

The reported frequency of permanent weakness (68%) and injuries from falls (67% of patients) is strikingly high. The rather severe incapacitation and the injuries by falling in the majority of patients have not yet been given sufficient attention. Our analysis suggests that the decline in activity with age is not due just to weakness and lack of physical endurance, but is also attributed to a fear of falling and the fear of provoking an episode. As permanent weakness is incapacitating and leads to decreased mobility and a reduced ability to participate in economic, social and family life, efforts have to be undertaken to improve the diminished quality of life: reversible weakness has to be improved and progression of fixed weakness to be slowed by medication that reduces the myoplasmic oedema and increases membrane excitability (3, 5).

Contrary to previous reports (1, 6), episodes occurred weekly to daily – even in HypoPP patients – and in the majority of cases (> 70%) they did not decrease in frequency or severity with older age. Over 80% of patients reported muscle pain and fatigue both of which have not been considered as typical symptoms hitherto. An unexpected number of patients (67%) reported muscle stiffness. While patients with HypoPP did not experience myotonia they may interpret the resistance of weak muscles to movement as stiffness, which may explain the high reported rate of stiffness in patients who do not have myotonia.

Our data is the first to report PMW in a genetically identified patient with paramyotonia congenita, a female in the 5th decade with the T1313M mutation. Additionally, our data is the first to report that PMW affects proximal muscles more severely than distal muscles, and the quadriceps muscle most of all. While PMW of the lower extremities affects an increasing amount of patients with age, PMW of upper extremities does not. We also could confirm previous reports (2, 3) that PP is associated with PMW in more than 60% of patients older than 40 years. (Table 3).

The survey indicated that self-managed exercise routine was superior to physiotherapy because more patients benefited and fewer patients deteriorated. Physiotherapy mustn't be too demanding; it has to be adapted to the individual capabilities and should recommend suitable mobility aids. It is the opinion of the authors, all of whom have extensive experience working with PP patients, that the intensity of physical therapy regimens should be jointly agreed upon by both physiatrist and patient with a tendency toward less rigorous rather than more intense sessions.

In agreement with the literature, age of onset of disease was primarily in childhood and puberty (74% of patients) (6), and permanent weakness increased with age (3). Also, as was expected, PC always manifested by the age of 2 yrs whereas the age of onset for other periodic paralyses was in puberty (~17 years). In none of the patients with adult onset (> 25 years) could a causative mutation be identified suggesting that some patients may be suffering from secondary forms of PP or from a not yet described entity. The overall mutation detection rate of 24% was only about half of that described in the literature. This may be due in part to incorrect clinical diagnosis and in part to unavailability or unaffordability of genetic testing. The calcium channel mutation Cav1.1-R528H (7) was twice as frequent as Cav1.1-R1239H (eight versus four patients) while all other mutations were rare.

Age of diagnosis was bimodal: the first peak was from patients diagnosed in childhood of which 82% of the parents were aware of the disorder because of positive family history, the second peak was from patients diagnosed after the age of 30 years mainly in patients who either have no known family mutation, or had adult onset.
Gender distribution was not even, but rather twice as many female as males participated in the study. While there are many possible explanations, based on the literature (1, 5) there is no reason to assume shortened lifespan of affected males. However, all 9 participants older than 70 years were female suggesting that males either may die earlier or are simply more reluctant to participate in such a study.

At the time of the survey, patients were taking a range of medications (Table 4). Some patients reported symptomatic relief from drugs that are not regularly recommended but may be beneficial. These may be of interest because they could point to possible treatment alternatives. For HypoPP there are two GABAergic drugs, baclofen and gabapentin; for HyperPP there are carbamazepine, fludrocortisone and the angiotensin I receptor antagonist, irbesartan; for PC there is a serotonin re-uptake inhibitor, paroxetine and for AS: triamterene.

### Table 4.
Medication history.

| HypoPP       | HyperPP       | PC              | AS              |
|--------------|--------------|-----------------|-----------------|
| acetazolamide | acetazolamide| Acetazolamide   | acetazolamide   |
| alactone     | albuterol    | hydrochlorothiazide | atenolol       |
| amiloride    | carbamazepine| mexiletine      | potassium       |
| baclofen     | fludrocortisone| paroxetine     | triamterene    |
| 3,4-diamino-pyridine | hydrochlorothiazide |              |                 |
| dichlorphenamide | irbesartan   |                 |                 |
| eplerenone   |              |                 |                 |
| gabapentin   |              |                 |                 |
| methazolamide|              |                 |                 |
| potassium    |              |                 |                 |
| propanolol   |              |                 |                 |
| pyridostigmine|              |                 |                 |
| topiramate   |              |                 |                 |
| triamterene  |              |                 |                 |
| verapamil    |              |                 |                 |

**Supplements**
| HypoPP          | HyperPP          | PC              | AS              |
|-----------------|------------------|-----------------|-----------------|
| calcium         | acetyl-l-carnitine| alpha lipoic acid| magnesium       |
| co-enzyme Q10   | calcium          | creatine monohydrate |                |
| creatine monohydrate | co-enzyme Q10    | Vitamin D3      |                |
| lecithin        | creatine monohydrate | Omega-3 fish oil |                |
| L-tyrosine      | lecithin         |                 |                |
| Omega-3 fish oil| Omega-3 fish oil |                 |                |
| progesterone cream | Vitamin B-group and D3 |             |                |
| taurine         | Vitamin B-group, C, D3 |             |                |

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**Footnotes**

*Clinical diagnosis: established through genetic identification of causative mutation or by clinical diagnostic procedures used prior to, or in addition to, genetic testing.

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