Medical Hypotheses 85 (2015) 749–753

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Size of quadriceps femoris may contribute to thyrotoxic periodic paralysis

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ARTICLE INFO

Article history:
Received 23 July 2015
Accepted 8 October 2015

ABSTRACT

Thyrotoxic periodic paralysis (TPP) frequently occurs on male individuals at their third and forth decades. The major site of involvement is the proximal muscles of lower limbs. Increasing evidence has shown that the occurrence of TPP is determined by multiple factors. We hypothesized that apart from hormonal fluctuations, skeletal muscle itself may explain for the age and sex variance as well. Our study was established to explore whether the size of lower limb skeletal muscles were related to TPP. We conducted a clinical experiment including 43 patients diagnosed with TPP (Group 1) and 39 pure hyperthyroidism individuals (Group 2). Current age, body mass index (BMI), thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), average girth of bilateral upper arm and thigh, physical activity level (PAL) were measured. We also adopted B mode ultrasound to quantify the muscle thickness (MT) of the major muscle involved in the disease, the quadriceps femoris (QF, including rectus femoris, RF; vastus intermedius, VI; vastus medialis, VM and vastus lateralis, VL). Patients were matched in TSH, FT4 and FT3. PAL was also statistically identical between groups. Age, BMI, thigh girth, the average of bilateral MT of QF were statistically different. After adjusting for age, BMI and girth, Group 1 still presented with larger MT of QF than Group 2, regardless of their current thyroid hormone level. There indeed exists an independent relationship between muscle thickness and TPP.

Introduction

Characterized by triad of acute limb muscle weakness, paroxysmal hypokalemia (shift of K^+ from extracellular space into intracellular space without being truly deficient of K^+) and hyperthyroidism, thyrotoxic periodic paralysis (TPP) mostly affects Asian oriental males of their third and forth decades. The biological predisposition to the disease has intrigued waves of scientific interests. So far, the elevated abundance and activity of Na^+ K^+ pump is recognized to be critical to the pathogenesis [1,2]. According to that, a series of elements which were potentially involved in the regulation of the pump had been investigated. Kung [3] took the lead to analyze genetic variance. They scanned five related genes *ATP1A1*, *ATP1A2*, *ATP1B1*, *ATP1B2*, *ATP1B4* and their upstream regulatory regions but failed to detect association between genetic polymorphism and the disease. Apart from genetic stimulation, hormones like thyroxine, insulin as well as testosterone can also act as strong activators of the pump. In 1994, Chan [4] reported glucose intolerance and hyperinsulinemia in TPP patients after 75 g glucose ingestion. In 2010, Wang et al. [5] processed such research to a more profound extent by evaluating thyroid hormone, insulin and total testosterone level at the same time. Significant increment were found in insulin along with total testosterone level while decreased FT4 FT3 in TPP patients was as well mentioned. Several years later, Yao [6] claimed a consistent result about testosterone during episodes of paralysis. Paradoxically, she found higher FT4 and FT3 in paralytic patients, which was different from Wang's discovery. Although researches on hormonal changes indeed shed light on the pathogenesis of TPP, a certain phenomenon aroused another doubt. Not all the hormone elevated hyperthyroidism males would develop paralysis. Therefore, the

Abbreviations: BMI, body mass index; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; MT, muscle thickness; PAL, physical activity level; QF, quadriceps femoris; RF, rectus femoris; TRAb, thyrotrophin receptor antibody; TSH, thyroid stimulating hormone; VI, vastus intermedius; VM, vastus medialis; VL, vastus lateralis.

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http://dx.doi.org/10.1016/j.mehy.2015.10.014
0306-9877/

disease is certainly a combination of several factors which together explain for the predisposition.

Hypothesis

In view of aforementioned, we hypothesized that the difference in skeletal muscle profile may play a role in the generation of TPP.

Rationale for the hypothesis

Limb muscle weakness is most commonly the first manifestation among TPP patients, making skeletal muscle the realm of interest. As the single largest pool of intracellular K^+, skeletal muscle plays a determinant role in K^+ homeostasis, mainly through the Na^+ K^+ ATP pump. In addition to hormonal stimulation, the pump itself is subject to a wide variety of regulators. According to early researches [7–9], skeletal muscle contains ~0.3 μmol Na^+ K^+ ATPase per kilogram skeletal muscle wet weight which predominately locate in the sarcolemma (1000–3500 per microns). Because the size of a muscle is closely related to the area of sarcolemma [10], therefore, it is reasonable to assume that the size of skeletal muscle, if without pathological infiltration of fat or connective tissue, could affect the quantification of Na^+ K^+ ATPase pump. As a matter of fact, young man do have larger size of locomotor muscles than age matched women or aging people [11,12]. Whether this phenomenon contributes to their predilection of TPP is still unknown. Unfortunately, current studies mainly focus on the genetic or hormonal effect, while the role of skeletal muscle itself is underestimated. Therefore, we came up with the idea of assessing morphological characteristics of the skeletal muscle, hoping to define whether they are related to TPP.

Method

Subjects

Based on medical records of West China Hospital of Sichuan University from 2010 to 2014, a total of 140 male patients were evaluated at the beginning, including outpatients, inpatients as well as patients from the emergency department. For TPP patients, the inclusion criteria consisted of a certain history of acute limb muscle weakness, hypokalemia and decreased thyroid stimulating hormone (TSH) with elevated free thyroxine (FT4), free triiodothyronine (FT3). Subjects who suffered from hyperthyroid/hypothyroid myopathy with long term muscle weakness, family periodic paralysis, renal tubular acidosis, hyperaldosteronism, hemiplegia, paraplegia, or any history of other metabolic or traumatic muscular disease, and recent reoccurrence of paralysis (within 6 months) were excluded. For control group, we included subjects with evidence of once aberrant thyroid function (decreased TSH, elevated FT4, FT3) without paralysis. Graves' disease (GD) was preferred which required information concerning either increased thyrotrophin receptor antibody (TRAb) level, ophthalmopathy or diffusively enlarged goiter. Individuals with simple thyroid associated ophthalmopathy, history of thyroidectomy due to malignancy or adenoma as well as subacute thyroiditis and pituitary hyperthyroidism were excluded.

Subjects were also required to provide identity card when being evaluated. In this way, we could guarantee that all individuals had the same ethnic background. 82 patients were finally included. Among them, 43 patients entered TPP group (Group 1) while the rest was assigned to the control group (Group 2). The study was a registered clinical trial with an identifier being NCT02287363. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Ethics Committee of Clinical Trials, West China Hospital, Sichuan University) and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was also obtained from all individual participants included in the study.

Clinical evaluation and blood sample test method

Clinical evaluation was performed by a certified investigator. Body height and weight were measured to the nearest 0.5 cm and 0.5 kg respectively. Body mass index was calculated from each subject's weight and height. The girth of extremities was measured at 15 cm above knee joint [13]. Blood sample was drawn immediately at enrollment. FT4, FT3 and TSH were determined using electro-chemiluminescence immunoassay (ECLIA Elecsys and Cobase immunoassay analyzer; Roche), which is the same test system and kit with West China Hospital.

Muscular ultrasonography

The main exposure of present study was muscle size, represented by muscle thickness (MT). A well trained sonographer consistently conducted measurements using B model ultrasound imaging device (Philips iu22 ultrasound system, Koninknijke Philips Electronics N. V.). A 12–5 MHz linear detector coated with considerable amount of water-soluble transmission gel was placed perpendicular to the tissue interface, especially to avoid compression of muscle surface. Participants were scanned in their supine position with arms and thighs fully relaxed. Quadriceps femoris (QF, including rectus femoris, RF; vastus intermedius, VI; vastus medialis, VM and vastus lateralis, VL) was selected as target muscle, not only because it can be identified most easily in ultrasound image, but also because they are the major muscle involved during paralysis [14]. For QF, since they formed a cambered surface, three different measurements from lateral to medial (Fig. 1) were taken at the axial plane of the midpoint between lateral condyle of femur and greater trochanter on the anterior surface of the thigh [15–18]. The greatest distance between the lowermost part of superficial facia and the uppermost part of bone was recognized as MT. The average of the three measurements were calculated to represent MT of QF.

We examined the intrarater reliability in healthy adults before measurement. The intraclass correlation coefficients (ICC[3.1]) was 0.92.

Physical activity level (PAL)

At enrollment, patients were interviewed with specific questions on the hours they spent in a typical day of the latest 12 months on vigorous activity (jogging, fitness dancing, swimming or manual construction work, etc.), moderate activity (yard work, bicycling on level ground, etc.), light activity (office work, fishing, grocery shopping, stroll etc;), sedentary activity (eating, watching television, mahjong, etc;) and periods of sleeping. An average metabolic equivalent score was derived from each activity [19], vigorous activity (8.0), moderate activity (4.0), light activity (2.0), sedentary activity (1.0), and sleeping (1.0). A model from Institute of Medicine [20] was adopted to calculate PAL, $PAL = 1 + \sum(METn - 1) \times 1.34 \times hn/24$, in which METn stands for the MET score of one activity; hn stands for self-reported hours spent on this kind of activity. This method was proved efficient for Chinese people in an earlier research this year [21].

Statistical analysis

SPSS Statistics version 19.0 (SPSS, Inc., Chicago, Illinois) was adopted to conduct statistical calculation. The two-tailed p value