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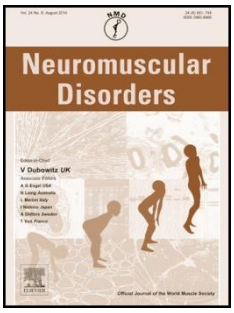

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Misdiagnosis is an important factor for diagnostic delay in McArdle disease

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Highlights:

- Correct diagnosis is rarely identified before adulthood in McArdle Disease
- A high frequency of misdiagnosis was seen in McArdle Disease

- Misdiagnosis occurred more frequent during childhood years
- Misdiagnosis delays the implementation of appropriate advice and management

Abstract

Diagnosis of McArdle disease is frequently delayed by many years following the first presentation of symptoms to a health professional. The aim of this study was to investigate the importance of misdiagnosis in delaying diagnosis of McArdle disease. The frequency of misdiagnosis, duration of diagnostic delay, categories of misdiagnoses and inappropriate medical interventions were assessed in 50 genetically confirmed patients. The results demonstrated a high frequency of misdiagnosis (90%, n=45/50) most commonly during childhood years (67%; n=30/45) compared with teenage years and adulthood (teenage: n=7/45; adult n=5/45; not known n=3/45). The correct diagnosis of McArdle disease was rarely made before adulthood (median age of diagnosis 33 years). Thirty-one patients (62%) reported having received more than one misdiagnosis; with the most common were "growing pains" (40%, n=20) and "laziness / being unfit" (46%, n=23). A psychiatric/psychological misdiagnosis was significantly more common in females than males (females 6/20; males 1/30; $p<0.01$). Of the 45 patients who were misdiagnosed, 21 (47%) received incorrect management.

This study shows that most patients with McArdle disease received an incorrect explanation of their symptoms providing evidence that misdiagnosis plays an important part in delaying implementation of appropriate medical advice and management to this group of patients.

Key Words: glycogen storage disease type V, McArdle Disease, growing pains, exercise intolerance, rhabdomyolysis, myoglobinuria

Abbreviations: AGSD-UK: Association for Glycogen Storage Disease; RM: Rhabdomyolysis; GSDV: Glycogen Storage Disease type V – McArdle disease; UK: United Kingdom

INTRODUCTION:

McArdle disease (GSDV) is an autosomal recessive disorder characterized by the absence of muscle glycogen phosphorylase. The enzyme deficit results in impaired muscle metabolism with symptoms such as exercise intolerance and muscle pain beginning in childhood. Muscle pain occurs within a few minutes of starting physical activity and can lead to muscle contracture and rhabdomyolysis (RM) if that activity persists or is more vigorous. Muscle contracture and RM in McArdle disease does not just follow exercise and can also be triggered by sustained isometric muscle contraction in everyday activities or 'unusual' circumstances.(1, 2) RM may result in potential life-threatening complications requiring urgent hospital admission such as compartment syndrome and acute kidney failure (table 1).

Early diagnosis, ideally when the individual is still a child, is important to facilitate learning the life skills required to manage the condition and prevent RM.(3) Timely diagnosis facilitates appropriate screening, management and prevention of known comorbidities associated with the condition such as sedentariness and obesity.(4) Currently, a correct diagnosis frequently occurs years after first presentation of symptoms.(5-8) This could, in part, be due to its rarity, as doctors might not be familiar with the clinical hallmarks of the condition such as the *second wind* phenomenon, which occurs after about 8-10 minutes of aerobic activity when the symptoms of exercise intolerance (tachycardia, myalgia and fatigue) disappear and the patient can exercise more freely.

To investigate the consequences of disease misdiagnosis in McArdle disease patients, a service evaluation was performed to assess the frequency of misdiagnosis, the duration of diagnostic delay, the categories of misdiagnoses and inappropriate medical interventions.

MATERIAL AND METHODS:

Clinical information from 50 consecutive patients with genetically confirmed GSDV (median age: 48.14; range: 16-73; 30 male, 20 female) was reviewed as part of service evaluation of a 'Nationally Commissioned Highly Specialized McArdle's Disease Service' based in London. The study was registered and approved by the Hospital's internal review board / audit committee. As this was a service evaluation, informed consent was not required. Detailed data on diagnosis and misdiagnosis is routinely collected as part of patients' assessment at the UK Specialised service. Further information is also available on NHS referral documentation and GP records / referral letter. Data related to onset of symptoms, year of diagnosis and related misdiagnoses, self-perception of GSDV symptoms and incorrect treatment prescription were collected via medical notes review and patients' personal experience reports using a standardised pre-agreed data extraction form. All data were anonymised, individual details and precise description of various misdiagnoses and incorrect treatment that could potentially identify an individual was omitted. In patients where more than one misdiagnosis had occurred, we reported data based on the age at the first misdiagnosis. Non-parametric data are summarised as median (range). Categorical data are summarised as percentages. Gender differences were assessed using Mann-Whitney U tests for continuous variables and Chi-squared tests for proportions.

RESULTS:

The frequency of misdiagnosis in patients with GSDV was 90% (n= 45/50). First misdiagnosis most frequently occurred during childhood years (67%; n=30/45), less frequently during teenage years or adulthood (teenage: n=7/45; adult n=5/45; not known n=3/45). However, ongoing or additional misdiagnoses were common through adult years with the median age of correct diagnosis being 33 years (range 6-70). The median delay in correct diagnosis of GSDV was 29 years (range 0 to 68). The median time from

symptom onset to receiving the first misdiagnosis was 3 years (range 0-67). The median time from the misdiagnosis to correct diagnosis was 23 years (range 1-62). There were no significant gender differences in any of these parameters. The diagnostic delay from the first symptoms to the correct diagnosis appeared to decrease over the decades (figure 1A). This decrease was associated with an increase in GSDV diagnostic rates with time (Figure 1B).

Thirty-one patients (62%) reported having received more than one misdiagnosis, with "growing pains" (40%, n=20) and "laziness / being unfit" (46%, n=23), representing the most common misdiagnoses (figure 2). A psychiatric/psychological misdiagnosis was significantly more common in females than males (females 6/20; males 1/30; $p<0.01$), but there weren't significant gender differences in the other categories. Notably six patients self-diagnosed their GSDV following library or internet searches. Of the 45 patients who were misdiagnosed, 21 (47%) received incorrect management with 13 (29%) receiving inappropriate exercise training advice (e.g. being advised to ignore symptoms of pain during exercise, or alternatively, being advised to avoid exercise altogether) and 12 (27%) received another medical intervention including antibiotic prescription, sternum surgery, tonsillectomy and invasive procedures such as cystoscopy.(2) Inappropriate exercise prescription that was too intense following a misdiagnosis of "laziness / being unfit" resulted in muscle damage and RM in a few patients. A few patients reported that, prior to diagnosis, bullying at school was a problem especially during physical education lessons, causing further emotional stress.

DISCUSSION:

A correct diagnosis is rarely identified before adulthood in people with GSDV with a median age of diagnosis of 33 years, despite symptoms starting at a median of 3 years of age. This study shows that most patients with GSDV will have sought medical assessment during childhood but received an incorrect explanation of their symptoms

providing evidence that misdiagnosis plays an important part in delaying correct diagnosis and implementation of appropriate medical advice. The median diagnostic delay in patients with GSDV was 29 years, which is in accord with age of diagnosis reported worldwide, usually between the 2nd to 5th decades.(5-8) Prevention of life-threatening complications such as acute RM, through timely diagnosis and appropriate management of the condition, has obvious health benefits, but also wider benefits to the healthcare economy by reducing the need for critical care admissions and avoiding costly treatment plans that may be associated with diagnostic errors.

In the UK, the time from first symptoms to diagnosis has decreased in recent decades. This could be explained by increased awareness of the condition and the development of a National service funded by the NHS. GSDV was first described in 1951.(9) Originally, diagnosis was made by forearm exercise test showing no rise in lactate and a muscle biopsy showing absent staining for muscle glycogen phosphorylase. Genetic diagnosis (*PYGM*) became available from the late 1990s. In the UK and northern Europe up to 85% of the GSDV population can be diagnosed by screening the two most common mutations (p.Arg50X and p.Gly205Ser), which is cheap and efficient costing only £120.(8). More recently, next generation sequencing panels for Glycogen Storage Diseases and disorders associated with RM have become available facilitating the genetic investigation of people presenting with exercise intolerance and/or recurrent RM.(10) In addition, the Nationally Commissioned highly specialised multi-disciplinary service for diagnosis and management of people with GSDV, first established in 2012, has had a positive impact in dissemination and training health care professionals. Establishing this highly specialized service has also resulted in faster diagnosis and, improved patient care with a documented reduction in McArdle disease related complications.(4) Public awareness of the condition has also improved as a result of the work of the Association for Glycogen Storage

Disease–UK (AGSD-UK) created in 1986.(11) AGSD-UK has provided support to patients in clinic, organised walking courses and produced videos and publications.(12)

Thus, improvements in the genetic diagnostic techniques, the creation of the highly specialised service and the AGSD-UK have positively contributed to the increase in early diagnosis. Measures to improve the diagnosis of GSDV such as dissemination and training were also implemented in Europe by the Euromac registry and network funded by the Health Programme of the European Union.(13-15)

Even though data presented here confirmed that people are being diagnosed with GSDV earlier in life, which seems to correlate with a decrease in the diagnostic delay, we are unable to confirm how many patients are still undiagnosed. Recall bias regarding personal experiences from patients' past medical history is also a limitation of this study. Data acquired by the Euromac registry will help to confirm the accuracy of the collected data and help to determine if the decreasing trend is consistent.

CONCLUSIONS:

In summary, misdiagnosis plays an important role in delaying GSDV diagnosis. Addressing misdiagnosis may be an issue of education since GSDV is a rare disorder. Efforts made to increase the awareness of the condition in the UK as summarised in this report suggest a positive impact in reducing the diagnostic delay.

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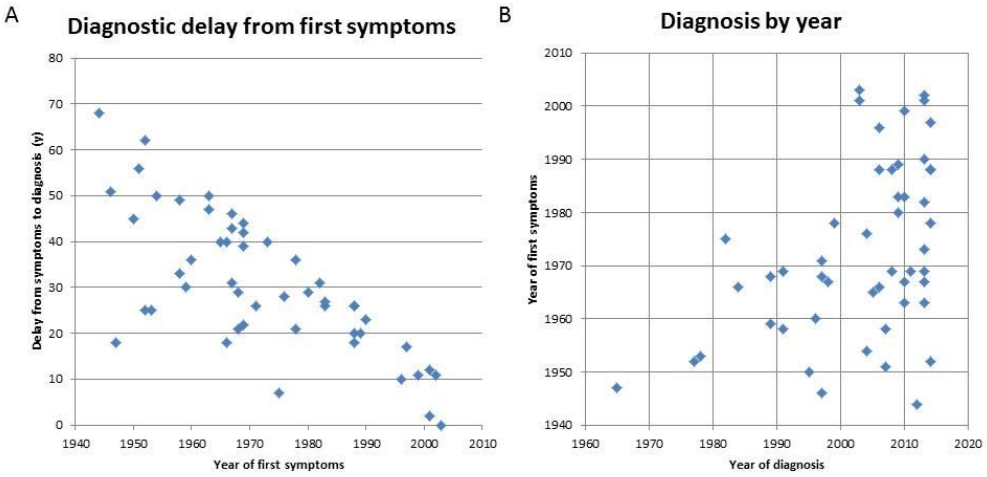

Figure 1A: Scatter plot of year of first symptoms versus delay from first symptoms to diagnosis. Diagnostic delay reduces as year of first symptoms increases; however patients with recent onset of symptoms who are yet to be diagnosed will not have been captured. There is a dramatic increase in number of diagnoses made after genetic testing became available in the late 1990s with 9 diagnoses made from 1990 to 2000; and 19 from 2000 to 2010. Figure 1B: Scatter plot of year of first symptoms versus year of diagnosis.

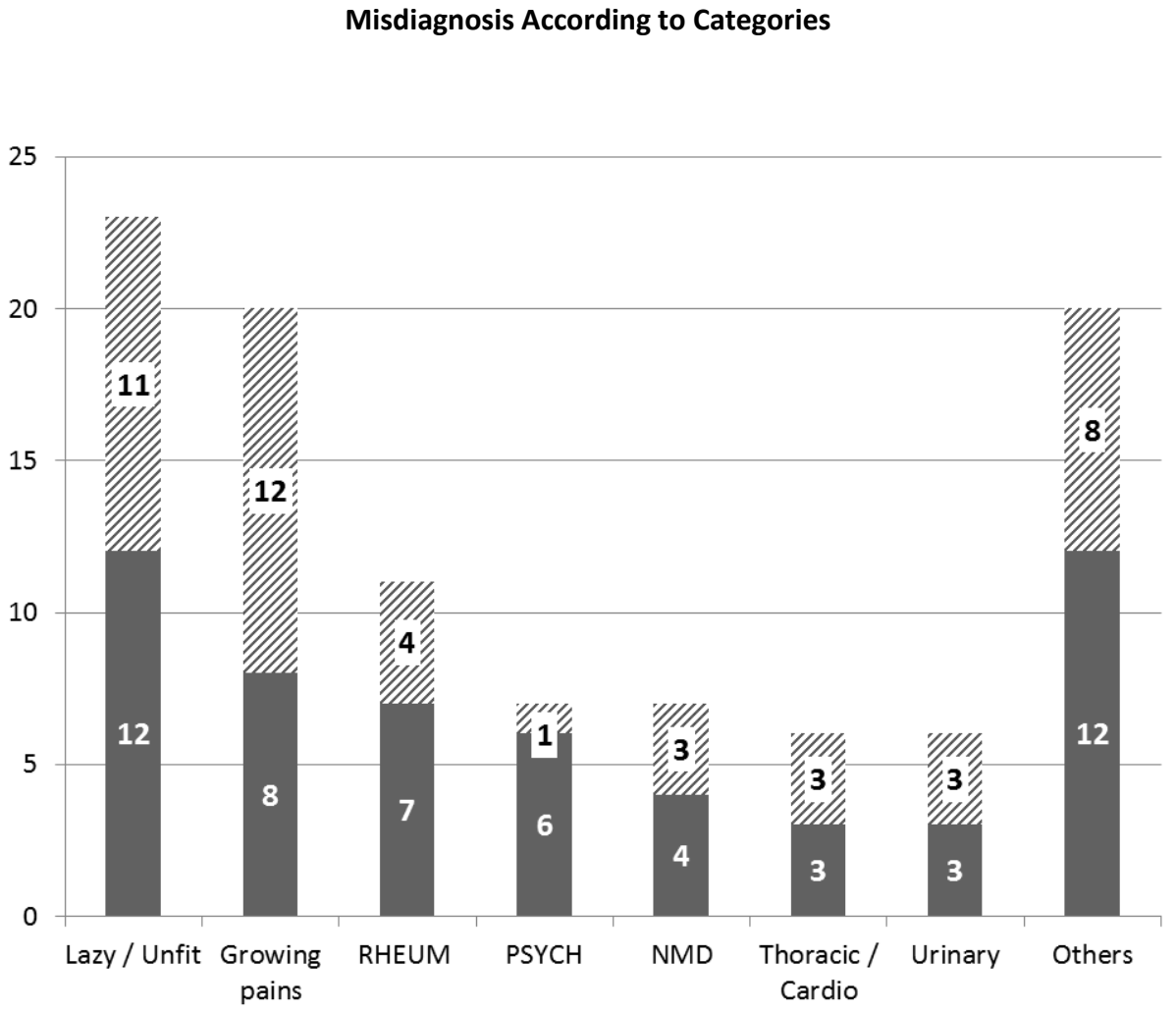

Figure 2 The total number of times misdiagnoses were reported by 45 genetically confirmed McArdle disease patients according to the categories of misdiagnosis and gender (female: dark grey, male: diagonal stripes). Several patients reported more than one misdiagnosis, and so the total frequency exceeded the number of assessed patients. RHEUM: rheumatic disorders; PSYCH: psychological conditions; NMD: neuromuscular diseases

Table 1: McArdle disease diagnostic features. CK: creatine kinase

McArdle Disease Features	**Medical History / Physical Exam**
Exertion Intolerance	Episodes of muscle pain and tachycardia at the beginning of any physical activity and during strenuous activity, isometric muscle contraction and/or resistance training. All skeletal muscles are involved. In children symptoms reported by parents include: • Infancy: Difficulty crawling more than a few yards • Toddlers: Wanting to be carried / or put in a push-chair all of the time, complaining of pain when walking • Children: o unable to run (maximum running distance 100m) o unable to keep up with peers o collapse/ vomiting during sporting activities
Muscle Contracture	Severe rigidity with associated pain (patients might report it as "muscle seizes up", "severe cramp"). Muscle contracture may affect any skeletal muscle for example the forearm with activities such as opening cans, picking up heavy pots, carrying shopping
Second Wind	During aerobic activity symptoms improve after 8-10 minutes The *second wind* can be identified with functional exercise testing with cardiac monitoring such as the 12 minute walk test or cycle ergometry (7, 16-18)
Episodes of Rhabdomyolyisis / Myoglobinuria	Severe muscle contracture followed by muscle swelling and pain; flu-like symptoms Discolouration of urine described as: tea, red wine or coca cola With severe episodes there may be collapse and acute renal failure CK is markedly raised (40,000-250,000 IU/L)
Additional Investigation	Baseline serum CK is usually raised (10-15 x normal) Serum urate is frequently raised Non-ischaemic forearm exercise test shows no significant rise in lactate DNA analysis: Initial screen for common mutations in Northern Europeans (p.Arg50X and p.Gly205Ser), Next tier Full *PYGM* sequencing Muscle biopsy rarely required: vacuolar myopathy, sub-sarcolemmal glycogen deposition and absent muscle glycogen phosphorylase activity