Axial myopathy: an overlooked feature of muscle diseases

Nanna Witting, Linda K. Andersen and John Vissing

Classically, myopathies are categorized according to limb or cranial nerve muscle affection, but with the growing use of magnetic resonance imaging it has become evident that many well-known myopathies have significant involvement of the axial musculature. New disease entities with selective axial muscle involvement have also been described recently, but overall the axial myopathy is unexplored. We performed a PubMed search using the search terms ‘myopathy’, ‘paraspinal’, ‘axial’ and ‘erector’. Axial myopathy was defined as involvement of paraspinal musculature. We found evidence of axial musculature involvement in the majority of myopathies in which paraspinal musculature was examined. Even in diseases named after a certain pattern of non-axial muscle affection, such as facioscapulohumeral and limb girdle muscular dystrophies, affection of the axial musculature was often severe and early, compared to other muscle groups. Very sparse literature evaluating the validity of clinical assessment methods, electromyography, muscle biopsy and magnetic resonance imaging was identified and reference material is generally missing. This article provides an overview of the present knowledge on axial myopathy with the aim to increase awareness and spur interest among clinicians and researchers in the field.

Introduction

Classically, myopathies are categorized according to limb or cranial nerve muscle affection, but with the growing use of MRI it has become evident that many well-known myopathies have significant involvement of the axial musculature (Kornblum et al., 2006; Kesper et al., 2009; Quijano-Roy et al., 2012). New disease entities with selective axial muscle involvement have also been described (Loseth et al., 2013), but overall the presence of axial myopathy among muscle diseases is unexplored. Paraspinal affection may be the first complaint in myopathies known for other typical manifestations such as facioscapulohumeral muscular dystrophy (FSHD1) or inclusion body myositis (sIBM). Conversely, dropped head or camptocormia may have many different aetiologies, complicating the diagnosis (Table 1).

There is a need to focus on axial myopathies to characterize disease expression, consequences and develop methods for clinical assessment and treatment strategies. This update attempts to raise awareness about myopathies with axial weakness, and will describe conditions with paraspinal involvement, and methods for assessment.

Keywords: axial; paraspinal; myopathy; rigid spine

Abbreviations: FSHD1 = facioscapulohumeral muscular dystrophy 1; GSDII = glycogen storage disease type II; MFM = Motor Function Measure

Correspondence to: Nanna Witting,
Department of Neurology
2081, Rigshospitalet,
Copenhagen, Denmark
E-mail: nanna.witting@regionh.dk

Copenhagen Neuromuscular Centre, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark
Definition and classification of axial myopathy

We included myopathies with sole or significant affection of the paraspinal musculature (Fig. 1), with or without more widespread muscle involvement. Myopathies with primary affection of other truncal muscles like serratus, latissimus dorsi or truncal muscles are not included. The axial myopathies are described according to whether axial myopathy is predominant, i.e. constitutes the major part of the myopathy, or rather is a part of more widespread myopathy, i.e. paraspinal myopathy is present, but other musculature is involved to a similar degree. The axial myopathies were furthermore subdivided according to age of onset and concomitant features (Table 1).

Identification of axial muscle involvement

Applicability and validity of clinically evaluation, muscle biopsy, EMG or MRI to qualify and quantify axial myopathy has been insufficiently studied. We discuss these methods, in the context of axial myopathy, below.

Clinical evaluation

When abnormal posture or severe atrophy of paraspinal muscles (Fig. 2) coexist with generalized myopathy, paraspinal myopathy is easily diagnosed. The paraspinal musculature, however, is embedded in bone and fatty tissue, which hampers clinical assessment, and axial myopathy is therefore often not clinically obvious (Fig. 2E). Moreover,
back pain rarely indicates axial myopathy (Dahlqvist et al., 2014). It is still an enigma whether spine rigidity is always related to axial weakness. Clearly, several axial myopathies with pronounced weakness have no associated rigidity, so weakness does not always lead to stiffness and reduced mobility, but the question is whether muscles are always weak when the spine is rigid. To discriminate between the various myopathies with paraspinal involvement phenotypic analysis can be used (Table 1). Also, taking a thorough history, including family history and motor development, is important.

Examination of axial myopathy

The literature evaluating assessment methods of paraspinal musculature is sparse. All methods described in this paper are therefore based on clinically evolved standards (Clarkson, 2000; Kendall, 2005).

Motor function scales

The Hammersmith Functional Motor Scale (HFMS) and the Motor Function Measure (MFM) are commonly used to assess neuromuscular disease. Both estimate function rather than specific muscles. The HFMS evaluates neck mobility/strength in 2/32 items and hip/spine mobility in one item. The MFM assesses the ability to roll from side to side, in addition to several other functions. Thus in the context of paraspinal myopathy, we find these scales too unspecific.

Figure 2 Clinical photos and MRI images of six cases with axial myopathy. (A) Patient with FSHD1. Note the sparing on the MRI of the most medial paraspinal musculature. (B) Patients with limb girdle muscular dystrophy type 2A. The MRI is from the lumbar region but no clear atrophy is noticed at clinical inspection. (C) Patient with autosomal dominant calpainopathy. MRI shows almost complete fat infiltration of the paraspinal musculature, just sparing the most medial parts. (D) McArdle disease with unusually severe axial myopathy. (E) Aetiologically unclassified axial myopathy with 20 years progressive axial weakness without rigidity or pain. Slight weakness and atrophy of proximal upper limbs and knee flexors. Abdominal muscle function preserved. Creatine kinase normal, myoglobin 231, muscle biopsy from the lateral vastus was myopathic with increased fibre size variability. Western blot normal. RYR1 normal. (F) Aetiologically unresolved axial myopathy with lifelong progressive and severe lumbar kyphoscoliosis present from 7 years of age. Limb strength normal. creatine kinase normal, myoglobin 244, biopsy from the lateral vastus myopathic with increased number of central nuclei. MRI displayed very localized axial myopathy. The patient later received surgery with thoraco-lumbar deses. The patient’s sister and father are reported to have similar symptoms. RYR1 normal. Note the selective involvement of the most medial paraspinal musculature. Informed consent was given by all patients.
Observation of mobility
Assessment of mobility is necessary to interpret muscle weakness and adds important diagnostic information. Figure 3A and B shows how lumbar flexion and extension mobility is examined, without hip joint interference. Lifting the antero-superior-iliac from the table, adds hip extension to back extension.

Figure 3C and E shows normal neck mobility in flexion and extension. If the chin is moved towards the chest in flexion the upper thoracic spine is involved (Fig. 3D).

Manual testing of muscle strength
To extend the back, the erector spinae is assisted by the latissimus dorsi, quadratus lumborum, and trapezius. Figure 3F shows how back extension is tested. Patients with strong back extensor muscles, but weak hip extensor muscles, will not be able to lift the trunk, and hip extensor strength should therefore be tested. If there is weak hip extension, pelvis stabilization will result in full back extension (Fig. 3G).

To extend the neck, the erector spinae is assisted by splenius capitis and cervicis, semispinalis capitis and cervicis, and upper trapezius. Figure 3H demonstrates evaluation of neck extension. The examiner provides pressure against the postero-lateral part of the head and the patient extends the neck with the face turned to the side being tested.

Test of muscle strength using a dynamometer
For clinical follow-up and assessments of treatment response, manual muscle testing is too insensitive. Dynamometry offers quantitative evaluation, but the reproducibility, validity, and sensitivity to change are largely undescribed for axial muscles.

Fixed dynamometry
Generally, the reliability of fixed dynamometry is high [intraclass correlation coefficient (ICC) 0.80–0.99] when testing limbs in healthy subjects as well as in neuromuscular disease (Brinkmann, 1994; Personius et al., 1994; Hoagland et al., 1997; Colombo et al., 2000; Bandholm et al., 2008) and fixed dynamometry is often referred to as the ‘gold standard’. Reliability of fixed dynamometry to measure back and neck strength has been evaluated using various methods (Peolsson et al., 2001; Roussel et al., 2008) and generally is high (ICC 0.98). Fixed dynamometry, however, is expensive, time-consuming, requires extensive training, lacks portability, and takes up substantial space. Also learning effects must be taken into consideration (Newton et al., 1993; Gruther et al., 2009).

Hand-held dynamometry
Hand-held dynamometry does not require much training, is cost-efficient and is portable. Hand-held dynamometry measures limb muscle strength reliably in both healthy and patient populations (Wang et al., 2002; Roy et al., 2004; Thorborg et al., 2010; Stark et al., 2011). However, the reliability of measuring strength in back and neck muscles is more questionable (Moreland et al., 1997). Our laboratory recently used hand-held dynamometry to assess back extension in patients with FSHD1 and healthy subjects (Dahlqvist et al., 2014) and experienced a ceiling effect in strong individuals where it was challenging to provide enough counter pressure. In accordance with this, high reliability seems to be limited to weak muscles (Brinkmann, 1994; Visser et al., 2003). In addition, our clinical experience is that those administering the test should be trained together to avoid high interrater variability.

Paraclinical examinations
Muscle biopsy
Paraspinal muscles are rarely sampled clinically, and normative data have not been published. Healthy paraspinal musculature has been described with ‘moth-eaten’ fibres, split fibres or type grouping in 10–15% of biopsies (Mannion et al., 1997a) and with cores in 37% of subjects with back pain, but no neuromuscular complaints (Mannion et al., 2000). Type 1 fibre predominance (60%) has also been reported (Mannion et al., 1997a, b, 2000) and a post-mortem study observed ‘neurogenic’ changes, type 2 fibre atrophy and a higher number of ragged red and cytochrome oxidase-deficient fibres in healthy paraspinal musculature compared to limb muscles (Wrede et al., 2012). This seemingly pathological histology may relate to the many tendons in paraspinal musculature, as muscle tissue in proximity to tendons can exhibit myopathic features. Also, the paraspinal musculature consists of intermingled small and larger muscles that presumably differ structurally. If performing a needle biopsy, it is impossible to know exactly which muscle(s) is biopsied. Ultrasound guided biopsy may be valuable, but has not been evaluated yet.

Paraspinal histology in myopathy may show pathology even if limb muscle biopsy is normal (Narayanaswami et al., 2000). Collectively, muscle biopsies in the clinical evaluation of axial myopathy can currently not be recommended because normative data for specific parts of the paraspinal musculature are lacking. One exception may be suspicion of isolated neck extensor myopathy as inflammation has not been reported in healthy subjects.

Electromyography
EMG is a widely available technique to assess muscle function, but the exact local examination paradigm varies and local reference material is therefore necessary. In the presence of reference material, EMG may potentially be a useful method to screen for involvement of the paraspinal musculature.

Magnetic resonance imaging
Increasing use of muscle MRI has led to a growing awareness of axial myopathy. MRI can quantify fat infiltration (Dixon, 1984) and visualize oedema. In addition, MRI may
Figure 3 Examination of mobility and muscle strength in the back and the neck. (A) Normal range of motion in the back flexion. (B) Normal range of motion in the back extension. (C) Normal flexion of the cervical spine. (D) Flexion of the cervical spine and the upper part of the thoracic spine. (E) Normal extension of the cervical spine. (F) Examination of muscle strength in the back extension Grade 0–1: the xiphoid process cannot be lifted and no muscle contractions are visible or palpable (Grade 0) or muscle contractions are visible or palpable (Grade 1). Grade 2: the xiphoid process is just lifted with arms by the sides. Grade 3: the patient can extend part of full movement. Grade 4: full movement with hands behind the lower back. Grade 5: full movement with hands behind the head. (G) Examination of muscle strength in the back extension; patient with weak hip extensor muscles. (H) Examination of muscle strength in the neck extension. (I) Examination of muscle strength in the back extension; using a hand-held dynamometer.
also disclose a characteristic pattern of involvement of the axial musculature such as a selective affection of medial or lateral parts of the erector spinae muscles (Fig. 2A and F) or disclose a characteristic combination of limb versus axial muscle involvement. The diagnostic value of such patterns with selective involvement of certain parts of the paraspinal myopathy has not been evaluated. In limb myopathies, however, selective muscle affection as shown by MRI can be an important diagnostic clue. The summary of myopathies with axial muscle involvement below describes most of the MRI studies evaluating paraspinal musculature. Most MRI studies of myopathy scan lower limbs selectively and in many, also more common, myopathies paraspinal musculature has not been investigated.

Myopathies with predominant axial involvement

Predominant axial myopathies usually have clinically evident paraspinal affection with rigid spine or abnormal posture. The most well-known predominant axial myopathy is probably selenoprotein deficiency characterized by rigid spine, scoliosis and respiratory insufficiency, often while still ambulatory (Jungbluth et al., 2011). MRI confirms selective involvement of paraspinal musculature (Mercuri et al., 2010; Quijano-Roy et al., 2012). Another classic, mostly axial, myopathy is due to mutations in the lamin A/C gene characterized by cardiac arrhythmias, proximal weakness, contractures and axial muscle involvement (Bonne et al., 2000; Quijano-Roy et al., 2012; Maggi et al., 2014). A more severe and earlier onset variant has pronounced dropped head and axial weakness (Mercuri et al., 2004; Quijano-Roy et al., 2008; Chemla et al., 2010; Prigogine et al., 2010).

Two metabolic myopathies: glycogen storage disease type II (GSDII, Pompe disease, acid maltase deficiency) and McArdle disease (glycogen storage disease type V) also may have pronounced paraspinal affection. GSDII usually has severe axial involvement at onset (Laforet et al., 2010; Salem et al., 2010; Hobson-Webb et al., 2011) whereas McArdle disease is characterized by dynamic symptoms at first, but in the fourth decade one-third develop permanent weakness, which can be selectively paraspinal (Quinlivan et al., 2010; Witting et al., 2014) (Fig. 2D).

Recently, a novel predominantly axial hereditary myopathy was coined with mutations in the ryanodine receptor 1 (RYR1) gene. Aberrations in RYR1 are responsible for several other myopathies. The axial myopathy phenotype is a progressive late-onset condition with pronounced lumbar hyperlordosis, cervical camptocormia, slight proximal weakness and myalgia (Loseth et al., 2013).

A relatively common inflammatory myopathy is the isolated neck extensor myopathy (INEM) with onset after age 60 (Katz et al., 1996; Kastrup et al., 2008; Muppidi et al., 2010). Muscle biopsy of the neck extensors in INEM is often without inflammation, but still, effect of steroid treatment is observed (Muppidi et al., 2010). EMG can show short and low-amplitude muscle potentials and spontaneous activity. MRI may demonstrate reversible oedema and contrast enhancement of the neck extensors (Gaeta et al., 2006).

Finally, radiation may, in ~11% of exposed, induce a predominant axial myopathy with a latency of, on average, 15 years. The myopathy respects the field of radiation and in the majority induces dropped head or other manifestations of axial myopathy (Ghosh and Milone, 2013b).

Myopathies with prominent paraspinal involvement as part of more widespread myopathy

In this group of myopathies paraspinal involvement may also be clinically evident in a number of cases. The hyperlordotic, scoliotic posture in Duchenne muscular dystrophy is well known and partially caused by hip extensor weakness, but MRI of erector spinae demonstrates fatty infiltration also in non-scoliotic boys, suggesting that axial weakness may predate the scoliosis (Zoabli et al., 2008). The majority of female carriers also have involvement of the paraspinal musculature (Tasca et al., 2012). Information is lacking regarding Becker muscular dystrophy.

Patients with FSHD1 may present with bent spine or camptocormia (Ghosh and Milone, 2015a). We examined 50 unselected FSHD1 patients clinically and with MRI, and the majority of patients had pronounced weakness of the back, correlating with paraspinal muscle fat infiltration, but not with back pain (Dahlqvist et al., 2014) (Fig. 2A).

Four and a half LIM 1 protein myopathies have different, but partly overlapping phenotypes (Quinzii et al., 2008; Windpassinger et al., 2008; Cowling et al., 2011) that all share rigid spine, scapular winging, cardiac and respiratory affection and asymmetry. Severe fatty infiltration of the paraspinal muscles has been demonstrated by MRI (Schreckenbach et al., 2013).

The collagen VI-related myopathies often have significant scoliosis in addition to contractures and limb myopathy and MRI may show paraspinal fatty infiltration. In addition, early onset titinopathies may have scoliosis or rigid spine (Chauveau et al., 2014).

In other instances, paraspinal involvement is not so clinically obvious. This is typically true for the limb girdle muscular dystrophies. Two MRI studies of patients with dysferlinopathy, showed that the erector spinae muscles was among the earliest and most severely fat-infiltrated muscles of all muscles studied (Nguyen et al., 2007; Kesper et al., 2009). In line with this, in calpainopathy patients, pronounced paraspinal involvement has been
observed on MRI and in the dominant forms axial affection can be a key feature (Liewluck et al., 2012). MRI of two patients with limb-girdle muscular dystrophy type 2D and with limb-girdle muscular dystrophy type 2I also demonstrated mild-to-moderate wasting and fatty infiltration of the paraspinals (Quijano-Roy et al., 2012).

Myotonic dystrophy type 1 is primarily a distal myopathy, but dropped head and camptocormia occur (Kocaaga et al., 2008; Dupeyron et al., 2010). Patients with myotonic dystrophy type 2 mostly have proximal limb myopathy. MRI, however, demonstrated that 8/15 type 1 and 4/5 type 2 patients had moderate-to-severe involvement of the erector spinae muscle (Kornblum et al., 2006).

The congenital myopathies caused by mutation in DNM2 (dynamin 2), TPM1 and TPM2 (tropomyosin 2 and 3) or RYR1 (recessive and dominant forms) have paraspinal affection as evidenced by MRI or clinically (Quane et al., 1993; Susman et al., 2010; Jarraya et al., 2012; Quijano-Roy et al., 2012; Schreckenbach et al., 2014). These are all early-onset myopathies and may have scoliosis or rigid spine.

Among the more recently defined myopathies, certain myofibrillar myopathies, valosin-containing peptide-related myopathy, MATR3 (matrin 3) gene and MYH7-related myopathies all may have axial involvement. The myofibrillar myopathies are genetically heterogeneous myopathies characterized by desmin-positive accumulations (Claeys and Fardeau, 2013). Cases with BAG3 and DES (desmin) mutations, and more infrequently, FLNC (filamin C) gene mutations, may lead to paraspinal weakness or rigid spine (Kley et al., 2007; Schramm et al., 2008; Selcen et al., 2009; Claeys and Fardeau, 2013), and CRYAB (αB-crystallin) mutations can result in an infantile onset phenotype with axial stiffness (Forrest et al., 2011).

Mutation in the gene encoding valosin-containing peptide induces adult-onset myopathy with distal, proximal or axial affection with dropped head (Shi et al., 2012). Frontotemporal dementia and Paget disease (Watts et al., 2004) may accompany the myopathy.

Mutation in the MATR3 gene (Muller et al., 2014) typically results in a myopathy with vocal cord palsy and distal limb weakness. Clinical back/neck weakness, however, occurs in about half, and MRI demonstrates paraspinal involvement in the majority (Muller et al., 2014). Mutation in the MYH7 (slow β-myosin heavy chain) gene causes Laing distal myopathy starting in the big toe and ankle extensors, but neck flexors may also be involved and 50% have scoliosis. MRI of paraspinal muscle has revealed atrophy and fat infiltration (Quijano-Roy et al., 2012; Park et al., 2013).

Among metabolic/mitochondrial myopathies, analysis of a large case series of neutral lipid storage disease showed that 33% had paraspinal muscle affection on MRI (Kaneko et al., 2014). Only a few cases of mitochondrial myopathy have been reported with axial involvement; a late-onset mitochondrial myopathy with predominantly paraspinal involvement due to tRNA^{Phe} mutation in mtDNA has been described (Sakiyama et al., 2011; Hiniker et al., 2014) and mutations in the thymidine kinase 2 (TK2) gene can also induce pronounced axial myopathy (Behin et al., 2012).

Poly-/dermatomyositis (PM/DM) and sporadic inclusion body myositis are auto-immune inflammatory myopathies with proximal limb weakness in PM/DM and finger flexors/ quadriceps affection in sporadic inclusion body myositis. Insertional hyperactivity on EMG of paraspinal muscles is common and dropped head or camptocormia has been reported in a number of cases (Hund et al., 1995; Goodman et al., 2012; Ma et al., 2013; Mattar et al., 2013). Sporadic late onset nemaline myopathy may also have camptocormia as part of a widespread myopathy.

**Differential diagnosis**

Pure motor diseases, such as motor neuron disease or myasthenia gravis, may present with a dropped head, but usually also have other features such as fasciculations, dysphagia, ptosis or fatigue. If those diseases are suspected, acetylcholine receptor antibody measurement/EMG is indicated. Parkinsonism may also present with abnormal posture and may have a myopathy. Special attention to classical parkinsonian features, cerebellar ataxia and autonomic symptoms is therefore needed. A DAT (dopamine transporter) scan may be helpful. Finally, osteochondrotic causes of abnormal posture can be evaluated by passive movement of the spine/neck where no constraint should be present in the case of a myopathy without rigid spine.

**Discussion**

Axial myopathy has received little attention in clinical practice and research, but based on the studies reviewed in this paper, it appears to be a grossly underestimated feature of many muscle diseases. When evaluated by MRI, paraspinal musculature is typically among the most severely affected muscles (Kesper et al., 2014) and poly-/dermatomyositis (PM/DM) and sporadic inclusion body myositis are auto-immune inflammatory myopathies with proximal limb weakness in PM/DM and finger flexors/quadriceps affection in sporadic inclusion body myositis.

How should axial myopathy be assessed? We suggest starting with mobility and strength testing followed by MRI. As paraspinal myopathy is not always obvious, clinical evaluation of paraspinal muscle strength should be performed in all patients suspected of myopathy. Evidence-based methods for clinical evaluation, however, need to be developed.

The role of EMG in the evaluation of axial myopathies is unsettled. EMG is an important tool to rule out differential diagnoses, but its applicability to examine paraspinal muscles is tainted by lacking local normative materials.
Biopsy of paraspinal musculature can likely be useful to diagnostic clarification in isolated neck extensor myopathy, but as with EMG, normative findings are lacking, and the limited knowledge we have on muscle morphology in paraspinal muscles, indicates that the histology deviates considerably from limb muscles (Mannion et al., 1997a, 2000; Wrede et al., 2012). Paraspinal muscle biopsy can therefore not generally be recommended.

Another unanswered question is whether axial muscle imaging can improve the diagnostic information compared to selective limb imaging. Pattern recognition is important when diagnosing muscle disease. Identification of a characteristic combination of axial and limb affection or a selective involvement of parts of the paraspinal musculature (Fig. 2) may therefore be valuable. Healthy paraspinal musculature shows age-dependent fatty infiltration and atrophy of the paraspinal musculature spreading from the deep to the superficial musculature, whereas the opposite happens in patients with FSHD1. Temporal evolution of paraspinal myopathy may therefore have diagnostic implications.

No systematic evaluations on how axial muscle weakness affects the patients have been made. It may lead to abnormal posture, but many, even with severe paraspinal myopathy, do not have abnormal posture. Pain is intuitively a consequence of weak paraspinal musculature or abnormal posture, but we recently showed a lack of correlation between degree of paraspinal muscle fat infiltration/weakness and intensity of back pain (Dahlqvist et al., 2014). This is in line with a dissociation between back pain and degenerative spinal disc and bone changes in otherwise healthy subjects (Bogduk, 2012).

Axial myopathy is an emerging field with major tasks of investigating distribution, diagnostic significance, clinical consequences, methods for evaluation and management issues ahead. A recent study could only identify the aetiology in half of cases with myopathic camptocormia as defined by EMG, creatine kinase, muscle histology and genetic studies (Ghosh and Milone, 2015a). As paraspinal myopathy is often not clinically evident, but can impose significant problems for the patient, attention to paraspinal involvement is warranted.

Funding
The Danish Council for Independent Research in Medical Sciences DFF – 4004-00438.

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15 April 2018

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