Review
Demystifying the spontaneous phenomena of motor hyperexcitability
J. Bashford a,b,e, W.K. Chan a, E. Coutinho a,b, F. Norwood b, K. Mills a, C.E. Shaw a,b

a UK Dementia Research Institute, Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK
b King’s College Hospital NHS Foundation Trust, Denmark Hill, London, UK

Article info
Article history:
Accepted 29 March 2021
Available online 13 May 2021

Keywords:
Fasciculation
Myokymia
Neuromyotonia
Surface EMG
ALS
Isaacs syndrome
Morvan syndrome
Neuronal hyperexcitability

Abstract
Possessing a discrete functional repertoire, the anterior horn cell can be in one of two electrophysiological states: on or off. Usually under tight regulatory control by the central nervous system, a hierarchical network of these specialist neurons ensures muscular strength is coordinated, gradated and adaptable. However, spontaneous activation of these cells and their axons can result in abnormal muscular twitching. The muscular twitch is the common building block of several distinct clinical patterns, namely fasciculation, myokymia and neuromyotonia. When attempting to distinguish these entities electromyographically, their unique temporal and morphological profiles must be appreciated. Detection and quantification of burst duration, firing frequency, multiplet patterns and amplitude are informative. A common feature is their persistence during sleep. In this review, we explain the accepted terminology used to describe the spontaneous phenomena of motor hyperexcitability, highlighting potential pitfalls amidst a bemusing and complex collection of overlapping terms. We outline the relevance of these findings within the context of disease, principally amyotrophic lateral sclerosis, Isaacs syndrome and Morvan syndrome. In addition, we highlight the use of high-density surface electromyography, suggesting that more widespread use of this non-invasive technique is likely to provide an enhanced understanding of these motor hyperexcitability syndromes.

2021 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Contents
1. Introduction ..................................................................................................... 1831
2. Phenomena of spontaneous motor hyperexcitability. ......................................................... 1831
2.1. Fasciculation ................................................................................................. 1831

Abbreviations: ALS, amyotrophic lateral sclerosis; CASPR2, contactin associated protein 2; CRD, complex repetitive discharge; CRMP5, collapsing response-mediator protein 5; EA1, episodic ataxia type 1; EEG, electroencephalography; EMG, electromyography; FP, fasciculation potential; GAD, glutamic acid decarboxylase; HDSEMG, high-density surface electromyography; IgLON5, immunoglobulin-like cell adhesion molecule 5; LGI1, leucine-rich glioma-inactivated 1; LMN, lower motor neuron; MD, myokymic discharge; MRI, magnetic resonance imaging; MuSK, muscle specific tyrosine kinase; ND, neuromyotonic discharge; NEMG, needle electromyography; NMUS, neuromuscular ultrasound; PNH, peripheral nerve hyperexcitability; SPiQE, surface potential quantification engine; UMN, upper motor neuron; VGKC, voltage-gated potassium channel complex.

Corresponding author at: UK Dementia Research Institute, Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK.
E-mail address: james.bashford@kcl.ac.uk (J. Bashford).

https://doi.org/10.1016/j.clinph.2021.03.053
1388-2457/© 2021 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
1. Introduction

During the second half of the twentieth century, an increased focus on patients with symptoms of peripheral motor hyperexcitability emerged. Alongside these discoveries, a constellation of similar terms arose, lacking consistent definitions and carrying a high risk of confusing the non-expert. Gutmann et al. reviewed the most widely used terms in 2001 (Gutmann and Libell, 2001), promoting the existence of myokymic and neuromyotonic discharges along a pathophysiological spectrum that is driven by abnormal voltage-gated potassium channel function. A key concept that holds as true today as it did then is that the clinical descriptions of fasciculation, myokymia and neuromyotonia are distinct from their electromyographic correlates of fasciculation potentials, myokymic discharges and neuromyotonic discharges. Notable advancements over the last two decades of the neurophysiological and immunological underpinnings of these clinical signs and their related clinical syndromes warrant an updated overview.

2. Phenomena of spontaneous motor hyperexcitability

2.1. Fasciculation

In the late 19th century, ‘fibrillar twitching’ was emphasized by Jean-Martin Charcot in his early descriptions of amyotrophic lateral sclerosis (ALS), although the term fasciculation was not introduced until 1938 (Table 1) (Denny-Brown and Pennybacker, 1938). Fasciculation describes the involuntary, irregular activation of a single motor unit (de Carvalho et al., 2017). Familiar to clinicians as a specific clinical sign of lower motor neuron impairment, it is observed in a broad spectrum of neurological conditions, such as ALS, spinobulbar muscular atrophy, peripheral neuropathies and multifocal motor neuropathy, as well as non-neurological syndromes, including hyperthyroidism and anxiety. Experienced by approximately 80% of the healthy population, particularly in lower limb muscles after exercise or caffeine, fasciculations in isolation are often a benign phenomenon (Blexrud et al., 1993).

Fasciculation potentials are distinguished electromyographically from other phenomena of motor hyperexcitability by their irregular, solitary nature (Fig. 2) (de Carvalho et al., 2017). Although occasional fasciculation potentials can occur as doublets, this should not be recurrent (distinguishing it from the recurrent doublets and multiplets seen as part of myokymic discharges). Mathematically, the firing of fasciculation potentials from the same motor unit obeys a Poisson distribution, while the intervals between successive fasciculation potentials follow an exponential distribution (Fitzurka and Tam, 1999, Kleine et al., 2008b).

Although fasciculations arise due to hyperexcitability of the neuronal membrane, there is conflicting evidence regarding their precise origin along the motor tract. Most studies support their origin in the lower motor neuron (de Carvalho and Swash, 2016b), either distally in the terminal arborisation of the axon, or proximally at the axon hillock near the soma. Collision techniques (Roth, 1982), fasciculation F-wave production (Roth, 1984) and use of spinal and local anaesthesia (Forster and Alpers, 1944) support the distal origin theory, whereas the firing of fasciculation pairs in the 40–100 ms range is consistent with the supernormal period at the axon hillock proximally (Kleine et al., 2008b). Sensory modulation of fasciculation potentials suggests complex inter spinal pathways can influence the fasciculation firing rate at the soma (de Carvalho et al., 2019). Supraspinal origins within the corticospinal tract are suggested by the synchrony of fasciculation potentials in muscle groups supplied by different peripheral nerves within the same myotome (Norris, 1965) and by the fact that fasciculations with a simple morphology can be driven by cortical stimulation with transcranial magnetic stimulation (de Carvalho et al., 2000, Mills, 1995). The almost exclusive occurrence of combined components of complex fasciculation potentials in ALS compared to spinobulbar muscular atrophy (a pure lower motor neuron syndrome) provides additional evidence for a supraspinal generator site for some fasciculations in ALS (Hirotta et al., 2000).

Motor neurons expend significant energy maintaining their neuronal membrane at the resting potential. This is achieved by the constant efflux of Na+ ions and influx of K+ ions in a ratio of 3:2 via the ATPase pump, thereby reversing the flow of cations that occurs during the course of an action potential (Park et al., 2017). If this pumping system fails in disease, then the resting neuronal membrane shifts to less negative potentials, nearer to the
threshold for action potential firing. Based on peripheral excitability testing in humans, there is convincing evidence of increased sodium conductance in ALS and spinobulbar muscular atrophy, as well as decreased potassium conductance in ALS (Bostock et al., 1995, Burke et al., 2001, Iwai et al., 2016, Kanai et al., 2006, Mogyoros et al., 1998, Nakata et al., 2006, Vucic and Kiernan, 2007). In combination, these effects make it more probable that an action potential may fire spontaneously, causing fasciculation. Coupled with the observation that energy-demanding fast-twitch motor units were more vulnerable to disease in murine models of ALS (Frey et al., 2000, Pun et al., 2006), it is probable that fast-twitch motor units begin to fasciculate before their slow-twitch counterparts.

2.2. Myokymia

Myokymia describes continuous, irregular quivering of the muscle (Denny-Brown and Foley, 1948), originating from the Greek words for muscle (=mys) and wave (=kyma) (Table 1). Considered a benign finding when isolated to the eyelid muscles (Banik and Miller, 2004), myokymia involving other facial nerve muscles is most often caused by demyelinating pontine lesions in multiple sclerosis but has also been reported in many other clinical contexts (Table 2) (Jacobs et al., 1994).

Limb myokymia classically results from radiation plexopathy or demyelination within either the intramedullary spinal cord (e.g. multiple sclerosis) or the peripheral nervous system (e.g. Guillain-Barré syndrome) (Albers et al., 1981, Mateer et al., 1983). It has also been shown to occur in association with nerve ischaemia (Albers et al., 1981), peripheral nerve injury (Albers et al., 1981, Medina et al., 1976), Charcot-Marie-Tooth neuropathy (Lance et al., 1979), thyroid disease (Sheaff, 1952), drug treatment (e.g., flunarizine) (Kizilay et al., 2011), vitamin B12 deficiency (D’Alessandro and Mulford, 2002), and toxins (e.g., gold, mercury, and the venom from the timber rattlesnake) (Brick et al., 1987, Caldron et al., 1987, Katrak et al., 1980, Zhou et al., 2014).

On EMG, myokymic discharges are characterised by bursts of doublets, triplets and multiplets at burst frequencies of 2–10 Hz (Fig. 2) (Gutmann, 1991). Generally, bursts that contain more spikes (up to 128 observed in a single burst) have lower inter-burst frequencies. The intra-burst spike frequency typically falls in the range of 5–62 Hz, is rarely greater than 100 Hz and never above 150 Hz (which would fall in the neuromyotonic range of intra-burst firing frequencies). In a single recording, multiple morphologies indicate the concurrent firing of several motor units. Radiation-induced limb myokymia has been reported to produce bursts of longer duration than other causes (Albers et al., 1981). Using high-density surface EMG, the inter-spike interval was

| Clinical sign | Year | Reference | Original language | EMG findings |
|---------------|------|-----------|-------------------|--------------|
| Fasciculation | 1938 | (Denny-Brown and Pennybacker, 1938) | English, fasciculation | FP |
| Myokymia | 1894, 1948 | (Schultze, 1894), (Denny-Brown and Foley, 1948) | German, myokymie, English, undulating myokymia (to differentiate from benign myokymia) | MD |
| Neuromyotonia | 1965 | (Mertens and Zschocke, 1965) | English (“Syndrome of continuous muscle-fibre activity”) | ND |
| Isaacs syndrome | 1961 | (Isaacs, 1961) | French, chorée fibrillaire de Morvan | FP, MD, ND |
| Morvan syndrome | 1890 | (Morvan, 1890) | English | FP, MD, ND |
| Cramp-fascillation syndrome | 1991 | (Tahnou et al., 1991) | English | FP, MD |

**Table 1**: First descriptions of clinical signs and syndromes related to spontaneous motor hyperexcitability. FP, fasciculation potential; MD, myokymic discharge; ND, neuromyotonic discharge.
shown to be longer at the end of a burst than at the start, postulated to occur due to the cumulative effect of late subexcitability changes during repetitive firing (Kleine et al., 2008a). Myokymic discharges disappeared after curare and succinylcholine administration, confirming their origin proximal to the neuromuscular junction (Isaacs, 1961). Myokymic discharges secondary to radiotherapy injury were extinguished by peripheral nerve block after six minutes, indicating a proximal origin at the site of neuronal injury (Albers et al., 1981). The same conclusion was drawn in a case of facial myokymia secondary to a brainstem glioma after applying a local nerve block at the stylomastoid foramen (Tenser and Corbett, 1974). It was hypothesised that the local mass effect in the brainstem interfered with interneuronal connections to the anterior horn cell. Given that myokymic discharges share similarities with the EMG findings seen in hypocalcaemic tetany and that parenteral calcium chloride injection abated the myokymia in Guillain-Barré syndrome (but not in multiple sclerosis or brainstem lesions), it has been speculated that reduced ionized calcium concentration in the peripheral neuronal microenvironment may contribute to the generation of myokymic discharges (Gutmann et al., 1986). Interestingly, only fast-twitch (type II) muscle fibres were glycogen-depleted in a case of acute myokymia in the gastrocnemius (Williamson and Brooke, 1972). Coupled with the observation that myokymic discharge potentials had dissimilar morphologies compared with voluntarily activated motor unit potentials (of slow-twitch subtype), it would suggest that myokymic discharges preferentially occur in fast-twitch motor units (Maddison, 2006).

Confusion can easily arise when one appreciates that clinical myokymia can exist in the absence of myokymic discharges on

Myokymic discharges disappeared after curare and succinylcholine administration, confirming their origin proximal to the neuromuscular junction (Isaacs, 1961). Myokymic discharges secondary to radiotherapy injury were extinguished by peripheral nerve block after six minutes, indicating a proximal origin at the site of neuronal injury (Albers et al., 1981). The same conclusion was drawn in a case of facial myokymia secondary to a brainstem glioma after applying a local nerve block at the stylomastoid foramen (Tenser and Corbett, 1974). It was hypothesised that the local mass effect in the brainstem interfered with interneuronal connections to the anterior horn cell. Given that myokymic discharges share similarities with the EMG findings seen in hypocalcaemic tetany and that parenteral calcium chloride injection abated the myokymia in Guillain-Barré syndrome (but not in multiple sclerosis or brainstem lesions), it has been speculated that reduced ionized calcium concentration in the peripheral neuronal microenvironment may contribute to the generation of myokymic discharges (Gutmann et al., 1986). Interestingly, only fast-twitch (type II) muscle fibres were glycogen-depleted in a case of acute myokymia in the gastrocnemius (Williamson and Brooke, 1972). Coupled with the observation that myokymic discharge potentials had dissimilar morphologies compared with voluntarily activated motor unit potentials (of slow-twitch subtype), it would suggest that myokymic discharges preferentially occur in fast-twitch motor units (Maddison, 2006).

Confusion can easily arise when one appreciates that clinical myokymia can exist in the absence of myokymic discharges on

---

**Table 2**

| Category                  | Association                                                                 |
|---------------------------|-----------------------------------------------------------------------------|
| Neoplastic                | Pontine tumour (Sharma et al., 1992, Tenser and Corbett, 1974)              |
| Inflammatory              | Vestibular schwannoma (Joseph and Rajshekhar, 2002)                         |
| Guillian-Barre syndrome   | (Van Zandyczke et al., 1982)                                               |
| Neurosarcomiosis          | (Sidropoulos et al., 2014)                                                 |
| Infective                 | Tuberculous meningitis (Aiguabellia et al., 2011)                           |
| Amyotrophic lateral sclerosis | (Whaley and Rublin, 2010)                                        |
| Spinocerebellar ataxia    | (Cancel et al., 1997, Taksyama et al., 1994)                                |
| Kufor-Rakeb syndrome      | (Inzelberg et al., 2018)                                                   |
| Multiple system atrophy   | (Blunt et al., 1997)                                                        |
| Familial dyskinesia and facial myokymia | (Chen et al., 2012, Fernandez et al., 2001)                                 |
| Acquired injury           | Cardiopulmonary arrest (Morris and Estes, 1981)                             |
| Congenital/developmental  | Syringobulbia (Raz et al., 1990)                                            |
| Obstructive hydrocephalus | (Sandyk, 1985)                                                              |
| Head and neck radiotherapy | – in conjunction with myokymia/neuropathy of lower cranial nerves (Rison and Beydoun, 2011) |
| Bell’s palsy              | (Bettoni et al., 1988)                                                      |

---

Fig. 2. Pathophysiologically characteristics of fasciculation potentials, myokymic discharges and neuromyotonic discharges. The respective origins along the lower motor neuron (proximal vs. distal) of peripheral hyperexcitability phenomena are depicted according to the underlying cause. The suspected pathological alterations in channel activity that are involved in the generation of peripheral hyperexcitability phenomena are represented. *Maximum fasciculation frequency in ALS was 360/min in a recent cohort study (Bashford et al., 2020a). **Although doublets occur rarely with intervals 5–100 ms, fasciculation potentials are predominantly solitary. ALS, amyotrophic lateral sclerosis; CASPR2, contactin associated protein 2; EC, extracellular; IC, intracellular; LGI1, leucine-rich glioma-inactivated 1; Na+, voltage-gated sodium channel; Na-K ATPase, sodium–potassium adenosine triphosphate-dependent pump; PNH, peripheral nerve hyperexcitability; VGKC, voltage-gated potassium channel complex. References for the information presented in this figure can be found throughout the main text (Sections 2.1–2.3).
EMG. Instead, high-frequency fasciculation potentials or neuromyotonic discharges can be seen, acting as mimickers of this clinical phenomenon. Conversely, myokymic discharges can be found when there is no myokymia clinically. The description of continuous motor unit activity has been used as an umbrella term in this context, including the EMG findings observed in stiff-person syndrome. However, this term lacks diagnostic specificity and should generally be avoided.

2.3. Neuromyotonia

First described by Isaacs in 1961 (Table 1) (Isaacs, 1961), neuromyotonia is an acquired autoimmune disorder characterised by hyperexcitability of the peripheral nerves (see Section 5.2). On EMG, neuromyotonic discharges are long, infrequent trains of motor unit potentials with very high intra-burst firing frequencies (150–300 Hz) and abrupt onset and offset (Fig. 2) (Gutmann and Libell, 2001). The maximum frequency is restricted by the absolute refractory period of the axonal membrane, which is approximately 3 ms (Maddison, 2006). Some authors have advocated a less clear distinction between the intra-burst frequency ranges found in myokymic discharges and neuromyotonic discharges, promoting the concept that these phenomena lie on a pathophysiological spectrum (Daube, 2001, Maddison, 2006).

Neuromyotonic discharges can be initiated by voluntary effort, movement of the needle during EMG examination, percussion of the nerve and/or electrical stimulation (Bednarlik and Kadañca, 2001, Torbergsen et al., 1996). The amplitude of the discharges typically wanes during a single burst (Gutmann and Libell, 2001). The discharges continued during spinal anaesthesia, proximal nerve block, and sleep, but were abolished by curare and botulinum toxin (Deymeer et al., 1998, Newsom-Davis and Mills, 1993). Cortical and peripheral nerve excitability tests were normal in patients displaying neuromyotonia (Park et al., 2014, Vucic et al., 2010), while macro-EMG confirmed smaller peak-peak amplitudes of neuromyotonic discharge potentials compared to voluntarily activated motor unit potentials (Arimura et al., 2005). All of these findings suggest that the origin of neuromyotonic discharges is distal in the terminal arborisation of the motor axon. This provides important mechanistic insight, especially when one considers that the motor nerve terminal is relatively unprotected by the blood–nerve barrier and thus susceptible to an antibody-mediated attack (Newsom-Davis, 2005). There is evidence in favour of an additional proximal generator site for neuromyotonic discharges that was ameliorated by immunomodulatory therapy (Santos et al., 2017).

Associated alterations in axonal nodal excitability have been demonstrated in patients with neuromyotonia, including a prolonged strength-duration time constant, which might signify relative depolarisation of the nodal membrane, paranodal demyelination and/or greater persistent sodium channel conductance (Maddison et al., 1999). This latter mechanism is supported by the effectiveness of sodium-channel antagonists (carbamazepine, sodium valproate and phenytoin) in the treatment of neuromyotonia in Isaacs syndrome (Vincent et al., 2018). However, a separate study reported no change in strength-duration time constant in patients with neuromyotonia, instead finding features consistent with a relative up-regulation of slow potassium channel conductance (Kiernan et al., 2001). This may occur in response to chronic potassium channel inhibition, which was suggested as a pathophysiological mechanism after in vitro culture with patient serum (Nagado et al., 1999, Sonoda et al., 1996). A predominance of slow–twitch fibres in the gastrocnemius of a patient with neuromyotonia suggested muscle fibres (and their associated motor units) may convert from fatigable fast–twitch fibres to more fatigue-resistant slow–twitch fibres as a result of continuous activation (Gutmann, 1996).

Pseudomyotonia is an important clinical association of neuromyotonic discharges, characterised by delayed relaxation after maximal voluntary contraction, typically elicited during a tight handgrip or eye closure (Ahmed and Simmons, 2015). Electromyographically, the neuromyotonic nature of pseudomyotonia should be accurately distinguished from the myotonic discharges of myotonia (see Section 3.2). To add further complexity to the nomenclature, paramyotonia (referring to ‘paradoxical’ myotonia) also produces myotonic discharges on EMG but can be distinguished from myotonia by its tendency to worsen on repeated exercise (in contrast to the ‘warm-up’ improvement typical of myotonia) (Stunnenberg et al., 2020). Handgrip pseudomyotonia leading to airway obstruction has also been reported (Levinson et al., 1976). Handgrip pseudomyotonia was exacerbated experimentally by hypoxia and was not responsive to peripheral nerve block (Oda et al., 1989). It was concluded that the likely origin of the causative neuromyotonic discharges was distal in the terminal arborisation of the motor axon.

3. Potential pitfalls

In this section, we outline potential pitfalls concerning the broader nomenclature of hyperexcitability phenomena and clarify overlapping terms that might elicit ambiguity. While an exhaustive list of terms can be found in Table 3, we focus on the most important of these in the text: fibrillations and positive sharp waves, myotonic discharges, myoclonus, and hemifacial spasm.

3.1. Fibrillations and positive sharp waves

Exclusively detected by needle EMG, fibrillations and positive sharp waves originate from acutely denervated muscles fibres (Mills, 2005). While it may take 7–10 days after denervation for a muscle fibre to become supersensitive to acetylcholine, thereby inducing fibrillations, it is reported that positive sharp waves may occur earlier (Kraft, 1991). Positive sharp waves are more commonly seen in healthy individuals than fibrillations, therefore the pathological significance of positive sharp waves without fibrillations is questionable (Kraft, 1991).

The distinction between fibrillations and fasciculations is a matter of size and there should be little cause for confusion between the two on needle EMG (Mills, 2005). A fibrillation represents a single muscle fibre, therefore its peak-peak amplitude does not exceed 300 μV. In contrast, a fasciculation represents firing of a motor unit with typical peak-peak amplitudes above 500 μV and may be as large as 20 mV due to compensatory reinnervation of motor units. Although fasciculations are often interpreted as an analogous sign of acute denervation in the context of ALS diagnosis (Costa et al., 2012), fasciculations should more correctly be interpreted as a sign of intrinsic neuronal hyperexcitability, which happens to coincide with active denervation in ALS.

3.2. Myotonic discharges

Myotonic discharges represent the electrophysiological correlate of myotonia, which is characterised clinically by delayed relaxation of skeletal muscles after voluntary activation, typically induced by forced handgrip or eye closure, or after percussion of the muscle (Hahn and Salajegheh, 2016). Myotonic discharges can be observed in dystrophic conditions (dystrophia myotonia, types 1 and 2) and non-dystrophic channelopathies (myotonia congenita, paramyotonia congenita and hyperkalaemic periodic paralysis), as well as in inflammatory myopathies, Pompe disease...
Table 3
Potential terminological pitfalls related to spontaneous motor hyperexcitability. CRD, complex repetitive discharge; EEG, electroencephalography; EMG, electromyography.

| Term                                      | Definition and clinical significance                                                                 | References                                                                 |
|-------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Arising from the muscle fibre             |                                                                                                        |                                                                           |
| Fibrillation                              | • Caused by spontaneous activity of acutely denervated muscle fibres.                                   | (Mills, 2005)                                                             |
|                                           | • Only detected by needle EMG.                                                                          |                                                                           |
|                                           | • Biphasic or triphasic.                                                                                 |                                                                           |
|                                           | • Monophasic.                                                                                            |                                                                           |
| Positive sharp waves                      | • Caused by mechanical perturbations of the acutely denervated muscle fibre membrane by a needle electrode. | (Kraft, 1991)                                                             |
|                                           | • Only detected by needle EMG.                                                                          |                                                                           |
| Complex repetitive discharge (CRD)        | • Characterised by a complex waveform. CRDs appear regularly at 3–60 Hz and are a sign of chronic neurogenic damage. | (Albers et al., 1981)                                                    |
|                                           | • Occur spontaneously or after electrical stimulation.                                                   |                                                                           |
|                                           | • Likely due to ephaptic transmission through muscle fibres.                                            |                                                                           |
| Motor unit potential induced repetitive    | • Analogous to CRDs, except they are time-locked to the voluntarily activated motor unit potential.      | (So et al., 2013)                                                         |
| discharge                                  | • Possibly due to ephaptic transmission through muscle fibres.                                          |                                                                           |
| Myotonic discharge                        | • Long train of discharges with waxing and waning frequency (20–150 Hz), giving it a characteristic ‘dive bomber’ sound on needle EMG. | (Mills, 2005)                                                             |
| Cramp potential                           | • Fast frequency (40–60 Hz) discharge with abrupt onset and offset, in association with clinical cramp. | (Katriji, 1990)                                                           |
| Spontaneous continuous motor unit single  | • 6 Hz frequency                                                                                        | (Posa et al., 2020)                                                       |
| discharges                                 | • Associated with a range of neurogenic conditions (amyotrophic lateral sclerosis, plexopathy, neuropathy). |                                                                           |
| Arising from the central nervous system    |                                                                                                        |                                                                           |
| Myoclonus                                  | • Sudden, shock-like, involuntary movements, which can be positive (‘muscle contraction above resting or background activity’) or negative (interruption of tonic muscle activity). | (Caviness and Brown, 2004)                                               |
| Palatal myoclonus                          | • Manifests as involuntary throat tensing and audible clicks.                                          | (Ito et al., 1993)                                                        |
|                                           | • Characterised by regular, tremor-like oscillations (~100 Hz) of pharyngeal, laryngeal and palatal muscles in association with brain stem lesions affecting the inferior olivary nucleus. |                                                                           |
| Polymyoclonus                              | • Myokymia can mimic the typical symptoms.                                                             |                                                                           |
| Continuous motor unit activity             | • Characterised by involuntary, small-amplitude jerky movements of the outstretched fingers and hands.   |                                                                           |
|                                           | • Classically associated with multiple system atrophy and cortically driven, as evidenced by back-averaging techniques on EEG. | (Kojovic et al., 2011, Rodriguez et al., 1994)                             |
| Syndromes affecting the cranial nerve territory |                                                                                                    |                                                                           |
| Hemifacial spasm                          | • Associated with bursts of up to 40 motor unit discharges at high frequencies (200–300 Hz).              | (Hjorth and Willison, 1973, Wilkins, 1991)                                 |
|                                           | • Typically caused by arterial compression of the facial nerve.                                          |                                                                           |
| Post-facial palsy synkinesis               | • Describes involuntary contraction of some facial muscles when intentionally trying to move another part of the face, occurring after recovery from facial palsy. | (Bacci and Kiernan, 2008, Öge et al., 2005)                               |
|                                           | • Involves myokymia-like discharges in orbicularis oris with intra-burst frequencies < 150 Hz occurring on ipsilateral eye blinking, but not spontaneously. |                                                                           |
|                                           | • Shortest inter-discharge intervals were 7–15 ms consistent with supernormal period of axonal membrane. |                                                                           |
|                                           | • Lengthening of ISIs at end of discharge to 20–40 ms consistent with late subexcitability.             |                                                                           |
| Blepharospasm                              | • A focal dystonia of orbicularis oculi, leading to eyelid spasms, excessive blinking and involuntary eye closure. | (Defazio et al., 2017, Grandas et al., 1988)                              |
|                                           | • Most common amongst women in their sixth decade.                                                      |                                                                           |
| Superior oblique myokymia                 | • A rare condition caused by intermittent unioocular microtremor of the superior oblique muscle, leading to oscillopsia and vertical/torsional diplopia. | (Rosenberg and Glaser, 1983, Susac et al., 1973)                           |
|                                           | • There is generally a good response to carbamazepine.                                                 |                                                                           |
|                                           | • Its labeling as a form of myokymia is likely to be a misnomer, as its electromyographic characteristics are more akin to hemifacial spasm. |                                                                           |
|                                           | • Rarely associated with oro-mandibular, cervical or laryngeal dystonias.                              |                                                                           |
| Ocular neuromyotonia                      | • Caused by nerve compression, cranial irradiation (abducens nerve), autoimmune disorders (myasthenia, thyroid eye disease), but can be idiopathic. | (Khimdras and Fraser, 2016, Soares-Dos-Reis et al., 2018, Stockman et al., 2018) |
| Features consistent with normal motor physiology |                                                                                                    |                                                                           |
| Doublet discharges                         | • Short-interval motor unit potential doublets (<10 ms) occurring at the start of voluntary firing, most often in fast-twitch, high-force motor units. | (Mrówczyński et al., 2015)                                               |
|                                           | • This boosts force during sustained contraction.                                                       |                                                                           |
| Functional neurological disorder           | • Functional hyperkinetic movements may be distinguished on EMG by a variable burst duration of at least 100 ms. | (Zutt et al., 2017)                                                       |
|                                           | • The positive indicators of distractibility and entrainment can be appreciated neurophysiologically.   |                                                                           |

and hypothyroidism. They can also be induced by drugs, such as cholesterol-lowering agents, colchicine and cyclosporine. Amongst the former group, statins and fenofibrate may mediate their myotonic side-effect via impairment of skeletal muscle chloride conductance (Pierno et al., 2009), necessitating their discontinuation in some patients.
Myotonic discharges are long trains of discharges with waxing and waning frequency (20–150 Hz), which produce a characteristic ‘dive bomber’ sound on needle EMG (Mills, 2005). They share a similar intra-burst frequency with myokymic discharges but should be distinguishable by a fluctuating frequency and absence of pairs, triplets or multiplets. In contrast, neuromyotonic discharges can be differentiated by a higher intra-burst frequency above 150 Hz. As the clinical distinction between pseudomyotonia (neurogenic) and myotonia (myogenic) can be challenging, the electromyographic description can reveal vital diagnostic insight (Parry-Jones et al., 1977).

3.3. Myoclonus

Myoclonic jerks are sudden, shock-like, involuntary movements, which can be positive (muscle contraction above resting or background activity) or negative (interruption of background muscle activity) (Caviness and Brown, 2004). Lacking anatomical specificity, myoclonus can originate from cortical, subcortical, brainstem, spinal and peripheral regions of the nervous system, and can be further classified as focal, multifocal, bilateral or generalised (Kojovic et al., 2011). Consequently, the potential aetiology is broad and can include post-anoxic brain injury (e.g. Lance-Adams), epilepsy (e.g. epilepsy partialis continua, juvenile myoclonic epilepsy), neurodegenerative disease (e.g. storage diseases, spinocerebellar ataxia, Alzheimer’s disease, subacute sclerosing panencephalitis), stroke, Creutzfeld-Jakob disease, toxins, and psychiatric conditions, including patient tolerance to repeated testing and monitoring. However, a review by the American Academy of Neurology initially considered SEMG an unacceptable clinical tool for diagnosing neuromuscular disease (Pullman et al., 2000). It was concluded that important diagnostic measurements (e.g. motor unit size and shape, interference pattern, and spontaneous activity) that are discernible by NEMG could not be reliably measured using SEMG. Also, SEMG had limited spatial resolution, was more susceptible to artefacts, and was more affected by subcutaneous adipose tissue, when compared to NEMG (Kuiken et al., 2003, Pullman et al., 2000). Subsequently, the American Association of Neuromuscular & Electrodiagnostic Medicine stated that SEMG could detect the presence of neuromuscular disease, but evidence to support its ability to distinguish between neuropathic and myopathic conditions was lacking (Meekins et al., 2008).

4. Methods of detection

4.1. Needle electromyography

Needle electromyography (NEMG) is an invasive diagnostic procedure for recording and analysing electrical signals from muscle fibres, using an intramuscular needle electrode (Rubin, 2019). Performed in conjunction with nerve conduction studies, NEMG is the current gold standard in the electrophysiological diagnosis of neuromuscular disease, including ALS and PNH syndromes (Drost et al., 2006, Fuller, 2005). It is accepted that the presence of fibrillation potentials and positive sharp waves in acutely denervated muscle fibres can only be detected using NEMG. While NEMG is a safe technique, a few challenges reduce its utility outside routine clinical settings. For example, the invasive nature of NEMG limits its use i) in children; ii) in uncooperative, anxious, or paralysed patients; iii) when recording multiple muscles simultaneously; and iv) when recording muscles over long durations (Menkes and Pierce, 2019, Pitt, 2012, Rubin, 2012). Furthermore, there is a small risk of iatrogenic local trauma, including bleeding, infection and nerve injury (Al-Shekhlee et al., 2003).

4.2. Surface electromyography

Surface electromyography (SEMG) is a non-invasive technique, by which myoelectrical signals can be recorded and analysed using surface electrodes placed on the skin overlying the muscle (Al-Mulla et al., 2011; Bashford et al., 2020c). SEMG confers several practical advantages over NEMG due to its non-invasive nature, including patient tolerance to repeated testing and monitoring. However, such a broad differential diagnosis, electrophysiological characterisation can aid localisation of the myoclonus. Cortical myoclonus can be identified on electroencephalography (EEG), while burst duration on EMG is typically < 100 ms for cortical myoclonus, >100 ms for subcortical or spinal myoclonus and < 50 ms for peripheral myoclonus (Zutt et al., 2017). In five cases of presumed myoclonus secondary to ADC5 gene mutations, EMG characteristics were in fact consistent with myoclonus and chorea, not myokymia (Tunc et al., 2017). We have captured and quantified carbamazepine-induced myoclonus using high-density surface EMG, which disappeared on discontinuation of the offending medication (unpublished data). Functional jerks resembling myoclonus are associated with longer burst durations on EMG (>100 ms) and a characteristic Bereitschaftspotential on EEG (Zutt et al., 2017).

4.3. Hemifacial spasm

This condition is typically caused by arterial compression of the facial nerve at its exit site from the pons but has also been reported in multiple sclerosis with or without a unilateral pontine demyelinating lesion (Marin Collazo and Tobin, 2018, Wilkins, 1991). It begins with spasms of orbicularis oculi before spreading to other ipsilateral facial muscles. The electromyographic findings differ from those of facial myokymia. In hemifacial spasm, the motor unit discharges fire in bursts of up to 40 at high frequencies of 200–300 Hz. There is observed synchronicity between different facial muscles that is not seen in facial myokymia (Hjorth and Willison, 1973). Ephaptic transmission between neighbouring motor neurons in hemifacial spasm means that stimulation of one branch of the facial nerve leads to activation of another branch, which is not a feature of facial myokymia. There can be crossed activation of contralateral facial muscles in hemifacial spasm, but not in facial myokymia. Despite these differences, it can be difficult to distinguish these two conditions electromyographically.

4.4. High-density surface electromyography

High-density surface EMG (HDSEMG) is a non-invasive method of measuring electrical muscle activity (Fig. 3), employing multiple closely-spaced electrodes (typically 52–64) arranged in a grid...
HDSEMG has shown superior spatial resolution and muscle coverage over longer durations in comparison with NEMG (Howard and Murray, 1992, van Dijk et al., 2010), improving discrimination between motor unit potentials (Bashford et al., 2020a; Drost et al., 2007). HDSEMG has been used in research for a variety of conditions, including ALS (Bashford et al., 2019, Maathuis et al., 2012), Isaacs syndrome (Kleine et al., 2008a), Duchenne muscular dystrophy (Nizamis et al., 2020) and post-polio syndrome (Shoseyov et al., 2017), as well as for evaluating normal swallowing function (Zhu et al., 2017) and lower back pain (Murillo et al., 2019). However, its usage has been restricted mainly to research and not clinical application (Drost et al., 2006). One such method, Surface Potential Quantification Engine (SPIQE), was developed as an automated analytical tool for the detection and quantification of fasciculation potentials in ALS patients, obtaining a classification accuracy of 88% (Bashford et al., 2019).

4.4. Neuromuscular imaging

The role of ultrasound in routine clinical diagnosis is well established, but its specific use in diagnosing neuromuscular disorders is relatively new (Pillen et al., 2008). In recent years, neuromuscular ultrasound (NMUS) has been increasingly utilised in the diagnosis of compression neuropathies, demyelinating neuropathies, and peripheral nerve trauma (Walker et al., 2004).

In a cohort of 81 ALS patients, NMUS demonstrated significantly better sensitivity at detecting fasciculations in the tongue, biceps brachii, and tibialis anterior, compared to NEMG (Misawa et al., 2011). The sensitivity and specificity of NMUS in the diagnosis of ALS was almost equivalent to that of NEMG, with NMUS showing significantly higher detection rates of fasciculations, while NEMG maintained its superiority at detecting fibrillations (Grimm et al., 2015). Interestingly, the combination of NMUS and NEMG improved diagnostic accuracy significantly, compared to NEMG alone. However, NMUS was unable to distinguish between stable and unstable fasciculations, a distinction that is likely to confer mechanistic insight and disease-monitoring value (de Carvalho et al., 2017). In a case of paraneoplastic neuromyotonia, NMUS detected subclinical neuromyotonic discharges secondary to lung carcinoma (Nishikata et al., 2017). Most recently, MRI has been used to detect fasciculation firing in ALS, providing precise anatomical detail of the motor unit exceeding the capabilities of NMUS (Whittaker et al., 2019).

5. Relevance to disease

The discovery of fasciculation, myokymia and/or neuromyotonia prompts consideration of a broad range of differential diagnoses (Table 4). In this section, we focus on amyotrophic lat-
eral sclerosis (ALS), peripheral nerve hyperexcitability syndromes, such as Isaacs and Morvan syndromes, as well as various inherited disorders associated with motor hyperexcitability.

5.1. Amyotrophic lateral sclerosis

The clinical hallmark of amyotrophic lateral sclerosis (ALS) is the coexistence of upper motor neuron (UMN) and lower motor neuron (LMN) impairment in the same body regions (Kiernan et al., 2011). The onset of disease can be in limb (~70% of cases), bulbar (~25%), or respiratory (~5%) muscles, followed by rapid and relentless spreading to other regions (Brown and Al-Chalabi, 2017, Kiernan et al., 2011).

On examination, ALS patients exhibit a variable combination of UMN signs (e.g. spasticity, hypertonia, extensor plantar response, brisk deep tendon reflexes and positive jaw jerk) and LMN signs (e.g. fasciculations, atrophy, hyporeflexia and hypotonia) (Kiernan et al., 2011). The identification of fasciculations, either by clinical examination (Howard and Murray, 1992), needle EMG (de Carvalho and Swash, 2013, Mills, 2010), or surface EMG (Bashford et al., 2011), is crucial. The detection of fasciculation doublets and the associated interval (~1838)

5.2. Peripheral nerve hyperexcitability syndromes

Isaacs syndrome, Morvan syndrome and cramp-fasciculation syndrome constitute a group of peripheral nerve hyperexcitability (PNH) disorders lying on a spectrum of disease severity (Fig. 4) (Hart et al., 2002). At the more severe end (Isaacs syndrome and Morvan syndrome), the defining clinical features include myokymia, neuromyotonia, fasciculations, cramps, muscle stiffness, pseudomyotonia and pseudotetany. In addition to these core characteristics, dysautonomia (hyperhidrosis, arrhythmia and blood pressure lability) and pain (neuropathic, muscular or other) are also frequent. Additional central nervous system involvement (insomnia, mood change, amnesia, hallucinations and confusion) defines Morvan syndrome (Abou-Zeid et al., 2012). There is a strong association with serum antibodies targeting specific components of the voltage-gated potassium channel (VGKC) complex, namely leucine-rich glioma-inactivated 1 (LGI1), contactin associated protein 2 (CASPR2) and contactin 2, thus confirming an immunological basis for these syndromes (Fig. 2) (Vincent et al., 2018). There is an association with other autoimmune conditions, particularly myasthenia gravis, but also dermatomyositis, Sjögren’s syndrome and systemic lupus erythematosus (Hart et al., 2002, Taylor, 2005, Xiao, 2017). The identification of a PNH syndrome can herald a range of benign and malignant neoplasms, mainly thymoma (often with coexistence of anti-acetylcholine receptor antibodies) and small cell carcinoma of the lung (Rana et al., 2012).

5.2.1. Isaacs syndrome (acquired neuromyotonia)

First reported in 1961 by Isaacs, this syndrome affects predominantly males (~67% of cases) and has a median age of onset of 55 years (Vincent et al., 2018). It should be noted that the classical Isaacs syndrome phenotype of muscle stiffness, limb neuromyotonia and hyperhidrosis typically lacks central nervous system involvement (unlike Morvan syndrome), although patients might experience mood and sleep disturbance secondary to the symptoms of peripheral hyperexcitability. Muscle activity persists during sleep, and may result in muscle hypertrophy, particularly of calf muscles (Sawlani and Katirji, 2017). Dysautonomic signs (e.g. hyperhidrosis, sialorrhoea, piloerection, and abdominal pain) and neuropathic pain are common, while other sensory manifestations (e.g. paresthesiae) are rare (Sawlani and Katirji, 2017). Unusual presentations include focal neuromyotonia mimicking Dupuytren’s contracture or swaps neck deformity of the fingers (Gantenbein et al., 2010, López Chiriboga et al., 2018, Srijithesh, 2013).
slow-transit constipation and intestinal pseudo-obstruction (Viallard et al., 2005); cold-induced pseudomyotonia of the bulbar muscles (Morales-Briceño et al., 2019); and, lower urinary tract symptoms (Gonzalez Primomo et al., 2018).

Isaacs syndrome has been reported to co-exist with other diseases, including ALS (Mantero et al., 2016), chronic inflammatory demyelinating polyradiculoneuropathy (Basiri et al., 2011, Odabasi et al., 1996), amyloid light-chain amyloidosis (Nardetto et al., 2016), haematological malignancy (Lahrmann et al., 2001, Liguori et al., 2000), and hypoparathyroidism (Zambelis et al., 2009). It has also been described after certain pharmacological treatments, including anti-tumour necrosis factor therapy (Belluzzo et al., 2014), penicillamine (Reeback et al., 1979), oxaliplatin (Wilson et al., 2002), pancreatic cancer treatment (Saadati and Saif, 2009) and the human papillomavirus vaccine (Cerami et al., 2013). A severe case occurred four weeks after a wasp sting (Turner et al., 2006).

Antibody testing has been established as an important component of the investigative work-up, however clinical presentation is...
variable and the immunological underpinnings of Isaacs syndrome remain incompletely understood. Almost half of patients (45%) with Isaacs syndrome had at least one antibody to LGI1, CASPR2 or contactin 2 (Vincent et al., 2018), suggesting that other, as yet unknown, antigenic targets might be of relevance to this disorder. While low-positive VGKC levels in the range 100–400 pM lacked specificity in a large retrospective cohort (Paterson et al., 2014), the titres found in those with isolated peripheral nerve involvement are usually within that range (contrary to the high titres seen in patients with CNS involvement). In a CASPR2-positive cohort of 38 patients, only 13% were classified clinically as Isaacs syndrome (instead, 42% presented with limbic encephalitis and 29% with Morvan syndrome), despite the fact that 57% had features of peripheral nerve hyperexcitability on neurophysiological assessment (van Sonderen et al., 2016). The presence of CASPR2 antibodies in the CSF is more specific for limbic encephalitis than Isaacs or Morvan syndromes (Joubert et al., 2016). The co-discovery of other antibodies in Isaacs syndrome, including those targeting collapsing receptors and/or contactin 2, and 40% were associated with a tumour (mainly thymoma) (Irani et al., 2012). Symptomatic treatment included carbamazepine, phenytoin, sodium valproate, lamotrigine and acetazolamide. Immunomodulatory therapy with plasma exchange and/or intravenous immunoglobulin produces a good response in most patients (Vincent et al., 2018). Caution is advised during anaesthesia, particularly with the use of non-depolarising muscle relaxants (e.g. rocuronium), which may require smaller doses than usual (Ginsburg et al., 2009).

5.2.2. Morvan syndrome

The diagnosis of Morvan syndrome puts emphasis on the presence of central and autonomic disturbances, in addition to peripheral hyperactivity (Fig. 4) (Irani et al., 2012). Central features include encephalopathy, insomnia, vivid complex hallucinations, delirium, spatial and temporal disorientation, and hyponatremia, while autonomic involvement can result in hyperhidrosis, fever, sialorrhea, constipation, arrhythmias, hypertension and weight loss (Demirbas et al., 2017, Masood and Sitammagari, 2021). In a cohort of 29 patients with Morvan syndrome, 93% were male. 79% had serum antibodies targeting at least one of CASPR2, LGI1 or contactin 2, and 40% were associated with a tumour (mainly thymoma) (Irani et al., 2012). Symptomatic treatment included carbamazepine, phenytoin, sodium valproate and levetiracetam, while 19/22 patients responded to immunotherapy (steroids, intravenous immunoglobulin, or plasma exchange).

5.2.3. Cramp-fasciculation syndrome

Cramp-fasciculation syndrome is at the least severe end of the PNH spectrum (Liewluck et al., 2014). Cramps, fasciculations and myokymia, without neuromyotonia or pseudomyotonia, are the core clinical features. Compared to Isaacs and Morvan syndromes, it is less frequently associated with VGKC-complex antibodies, tumours and the requirement for immunomodulatory therapy (Fig. 4). It lacks central nervous system involvement, however some patients report dysautonomia in the form of hyperhidrosis. Carbamazepine remains the mainstay of symptomatic treatment (Tahmoush et al., 1991).

The electrophysiological correlate of cramp is the afterdischarge, which can be elicited in abductor hallucus in response to repetitive nerve stimulation (four pulses at 2–100 Hz) of the tibial nerve (Bodkin et al., 2009, Liewluck et al., 2014). Although neuronal hyperexcitability is almost certainly the common mechanism behind the generation of fasciculation potentials and cramp afterdischarges, quantification of the relationship between fasciculation potential frequency and afterdischarge duration warrants further investigation. It is emphasised that benign fasciculation syndrome is distinct from cramp-fasciculation syndrome and is most likely due to a nervous system at the hyperexcitable end of normal motor physiology (Blexrud et al., 1993). Superaed health anxiety can intensify the morbidity associated with benign fasciculation syndrome (Blackman et al., 2019).

5.3. Inherited disorders causing motor hyperexcitability

Caused by point mutations in the KCNA1 gene on chromosome 12, episodic ataxia type 1 (EA1) is characterised by frequent spells of gait imbalance and upper limb incoordination, typically lasting about 15 minutes, as well as interictal myokymia of skeletal muscles (Graves et al., 2014, Hasan and D'Adamo, 2010, Jen et al., 2007). EMG may be needed to reveal subclinical myokymia. During an attack, a range of other symptoms may be present, including vertigo, blurred vision, diplopia, dysarthria, weakness, tremors, and diaphoresis (Graves et al., 2014). Attacks can be triggered by emotional stress, startle or exertion, and onset is typically during childhood or early adolescence with reports of some attacks abating in adulthood (Brunt and van Weerden, 1990). The frequency of ataxic episodes can be improved by phenytoin or acetazolamide (Hasan and D'Adamo, 2010). Excitability testing in EA1 showed increased superexcitability and threshold electrotonus changes (Tomlinson et al., 2010).

It is noteworthy that episodic ataxia type 2 (due to CACNA1A mutations) does not cause myokymia (Jen et al., 2007). Mutations in KCNA1 or KCNQ2 can lead to familial neuromyotonia (Palace et al., 2007), while KCNQ2 mutations are also reported to cause benign familial neonatal convulsions and myokymia (Dedek et al., 2001). Clinical overlap between neuromyotonia and a motor–predominant, axonal Charcot-Marie-Tooth neuropathy exists as a result of recessive mutations in histidine triad nucleotide binding protein 1 (HINT1) (Peeters et al., 2017). Myotonia congenita (caused by CLCN1 chloride channel mutations; mode of inheritance either dominant [Thomsen disease] or recessive [Becker disease]) and paramyotonia congenita (caused by SCN4A sodium channel mutations) are briefly mentioned to highlight their distinctly myopathic nature, warranting diagnostic consideration in patients with delayed relaxation of muscles and an appropriate family history (Hahn and Salajegheh, 2016).

6. Conclusion

The study of motor hyperexcitability phenomena has appealed to the curious clinician for many decades. Despite the vast, often bewildering, array of terms that have emerged, we have sought to provide a pragmatic and cohesive overview of the core entities: fasciculation, myokymia and neuromyotonia. With features supporting their existence along a pathophysiological spectrum, further characterisation and quantification of these phenomena are warranted in a range of immunological, inherited and neurodegenerative diseases. Non-invasive techniques confer the necessary attributes to monitor these conditions frequently and expansively in a greater cohort of patients. Neurophysiological dissection in this way may provide the objective, quantitative tools required for efficient biomarker development and therapeutic monitoring.
Fundamentally, we hope this approach will enhance the drive towards novel treatments for several groups of patients, who are all in desperate need of symptomatic relief and, ultimately, a cure.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

JB acknowledges funding from the Medical Research Council and Motor Neurone Disease Association (Lady Edith Wolfson Clinical Research Training Fellowship; MR/P000983/1), Sattaurpur Charitable Foundation and UK Dementia Research Institute. WKC contributed during his MSc qualification in Clinical Neuroscience. EC received funding through a clinical fellowship from the MRC Centre for Neurodevelopmental disorders.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.03.053.

References

Abou-Zeid E, Boursouliau LJ, Metzzer WS, Gundogdu B. Morvan syndrome: a case report and review of the literature. J Clin Neuromuscul Dis 2012;13(4):214–27.

Ahmed A, Simmons Z. Isaacs syndrome: A review. Muscle Nerve 2015;52(1):5–12.

Aguilera M, Gascón-Bayart J, Montero J, Santin M, Peña C. Hyperexcitability of the facial nerve in tumourous meningiitis. Acta Neurol Belg 2011;111(3):245–8.

Al-Mulla MR, Sepulveda F, Colley M. A review of non-invasive techniques to detect and predict localised muscle fatigue. Sensors (Basel) 2011;11(4):3545–94.

Al-Shekhlee AE, Sattaripour S, Hirst AR, Lord CM, Blackman G, Cherfi Y, Morrin H, Ellis CM, Bashford J, Ruths F, David AS. The association between benign fasciculations and facial myokymia. Front Neurol 2016;7:270–72.

Alvarez N, Hirth C, Al-Jamal J, Anand K, Yen AW, Zhang HY, Nunn J, De Seze L, de Carvalho M. Lower motor neuron dysfunction in ALS. Clin Neurophysiol 2019;130(7):1083–90.

Albers WE, Allen AA, Bastron JA, Daube JR. Limb myokymia. Muscle Nerve 1981;4(6):494–504.

Antiotti M, Frassinetti F, Cozzolino D, Rinieri M, Jankovic J. Motor unit dysfunction in amyotrophic lateral sclerosis: a systematic review. J Neurol Neurosurg Psychiatry 2014;85(1):35–42.

Arimura K, Arimura Y, Ng A, Uehara A, Nakae M, Osame M, Stålberg E. The origin of spontaneous discharges: unusual electrophysiological pattern in acquired neuromyotonia. J Neurol 2003;250(5):517–26.

Albers WE, Allen AA, Bastron JA, Daube JR. Limb myokymia. Muscle Nerve 1981;4(6):494–504.

Antozzi C, Frassoni C, Vincent A, Regondi MC, Andreetta F, Bernasconi P, Ciano C, de Carvalho M, Swash M. Fasciculation potentials and earliest changes in motor unit discharges: unusual electrophysiological pattern in acquired neuromyotonia. J Neurol Neurosurg Psychiatry 2005;76(8):1835–9.

Apfelberg BD, Kiernan MC, Bostock H. Excitability of human axons. Clin Neurophysiol 2009;26(1):45–9.

Ashcroft DM, Watanabe M, Tarasov LA, Costigan M, Fotherby S, Simon J, McLean A, Smith MC. Inherited myokymia limited to the eyelid is a benign condition. J Neurol Neurosurg Psychiatry 2011;82(9):859–61.

Azizova I, Plassman R, Putzko E, Deitrich TP, Gharabelli SM, Scherqualo M, Stålberg E. Quantification of motor unit discharges in idiopathic amyotrophic lateral sclerosis: evidence for peripheral nerve origin. Neurology 1987;37(9):1545–6.

Baker DM, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2000;1(5):293–9.

Longo DL, Brown RH, Al-Chalabi A. Amyotrophic Lateral Sclerosis. N Engl J Med 2017;377(2):162–72.

Bodkin CL, Kennelly KD, Boylan KB, Crook JE, Heckman MG, Rubin DI. Defining density surface EMG: a systematic review. J Electromyogr Kinesiol 2006;16(5):466–7.

Bruck JW, Gutmann L, Jurgens R, Riggs JE. Timber rattlesnake venom-induced myokymia: evidence for peripheral nerve origin. Neurology 1987;37(9):1545–6.

Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2000;1(5):293–9.

Brown LW, Al-Chalabi A. Amyotrophic Lateral Sclerosis. N Engl J Med 2017;377(2):162–72.

Caldron PH, Wilbourn AJ, Bravo EE, Mitumoto H. Gold myokymia syndrome. A rare toxic manifestation of chrysotherapy. Cerebrovasc Dis 2004;17(3):225–5.

Cancel C, Durr A, Didierjean O, Imbert G, Burck K, Lezin A, Belal S, Benomar A, Abadabendib M, Vial C, Guimaureses J, Cheneiwiss H, Stevanin G, Yvert G, Abbans N, Saudou F, Lebre A-S, Yahyaoui M, Hentati F, Vernant J-C, Klockgether T, Mandel J-L, Agid Y, Brice A. Molecular and clinical correlations in spinocerebellar ataxia type 7. A case study of 32 families. Hum Mol Genet 1997;6(5):799–15.

Caviness JN, Brown P. Myokonium: current concepts and recent advances. Lancet Neurol 2004;3(10):598–607.

Cerami C, Corbo M, Piccolo G, Iannacce S. Autoimmune neuromyotonia following neonatal human papilloma virus vaccination. Muscle Nerve 2013;47(3):466–7.

Chen YZ, Matsushima MM, Robertson P, Rieder M, Girajaraj S, Antonacci F, et al. Autosomal dominant familial dyskinesia and facial myokymia: single exome sequencing identifies a mutation in adenyl cyclase 3. J Neurol Clin Neurosci 2012;69(5):563–5.

Costa J, Swash M, de Carvalho M. Awaji Criteria for the Diagnosis of Amyotrophic Lateral Sclerosis A Systematic Review. Arch Neurol 2012;69(11):1410–6.

D’Ambrosio AM, Mulford CJ, Bruni MC. Invasive case of electrophysiologic recorded myokymic potentials: a case report. Arch Phys Med Rehabil 2002;83(5):727–9.

Daube JR. Myokymia and neuromyotonia. Muscle Nerve 2001;24(12):1711–2.

de Carvalho M, Kiernan MC, Swash M. Fasciculation in amyotrophic lateral sclerosis: origin and pathophysiological relevance. J Neurol Neurosurg Psychiatry 2017;88(9):773–9.

de Carvalho M, Miranda PC, de Lourdes Sales Luiz M, Duca-Soares E. Neurophysiological features of fasciculation potentials evolved by transcranial magnetic stimulation in amyotrophic lateral sclerosis. J Neurol 2000;247(3):189–94.

de Carvalho M, Swash M. Fasciculation potentials and earliest changes in motor unit physiology in ALS. J Neurol Neurosurg Psychiatry 2013;84(9):963–8.

de Carvalho M, Swash M. Fasciculation discharge frequencies in amyotrophic lateral sclerosis and related disorders. Clin Neurophysiol 2016a;127(5):2257–62.

de Carvalho M, Swash M. Lower motor neuron dysfunction in ALS. Clin Neurophysiol 2016b;127(7):2670–81.

de Carvalho M, Turkman A, Pinto J, Swash M. Modulation of fasciculation frequency in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2016;87(2):226–8.

de Carvalho M, Turkman A, Swash M. Sensory modulation of fasciculation discharge frequency. Muscle Nerve 2010;39(6):688–93.

Dedek K, Kunath B, Kanaunara C, Reuner U, Jentsch TJ, Steinleink OK. Myokymia and neonatal epilepsy caused by a mutation in the KCNQ2 K+ channel. Proc Natl Acad Sci U S A 2001;98(21):12272–7.

Defazio G, Hallert M, Jonnah HA, Conte A, Berardelli A. Blepharospasm 40 years later. Mov Disord 2017;32(4):498–509.

Demirbas S, Aykan MB, Zengin H, Mazzan S, Saglam K. Morvan syndrome: a rare cause of syndrome of inappropriate antidiuretic hormone secretion. Cmaj J 2010;182(3):351–5.

Denny-Brown D, Foley J. Myokymia and the benign fasciculation of muscular cramps. Tramps Assoc Am Physic 1948;61:88–96.

Denny-Brown D, Pennybacker JF. Fibrillation and fasciculation in voluntary muscle. Brain 1938;51(3):311–2.

Deymeyer F, Oge AE, Serdaroglu P, Yazici J, Ozdemir C, Baslo A. The use of botulinum toxin in localizing neoromotonia to the terminal branches of the peripheral nerve. Brain 1993;116(8):1835–9.

Drost G, Kleine BU, Stegemann DF, van Engelen BG, Zwarts MJ. Fasciculation potentials in high-density surface EMG. J Clin Neurophysiol 2007;24(3):301–7.

Drost G, Stegemann DF, van Engelen BGM, Zwarts MJ. Clinical applications of high-density surface EMG: a systematic review. J Electromyogr Kinesiol 2006;16(6):586–602.

Falace A, Striano P, Manganeli F, Coppola A, Striano S, Minetti C, Zara F. Inherited myokymia: a clinical and genetic study of a family. Neuromuscl Disord 2007;17(1):23–7.
From the given text, we can extract a few key points:

1. Joseph BV, Rajshekhar V. Facial myokymia as a presenting symptom of vestibular schwannoma. J Neurol Neurosurg Psychiatry 2002;70(3):369–70.

2. Kijfyz A, Emkecki B, Gungor H, Uyyal O, Sh J. Fluorinized-induced fasciculation-myokymia. J Clin Neurosci 2011;18(12):246–7.

3. Kleine BU, Stegeman DF, Hart I. The instability properties of motor axons in patients with spontaneous motor unit activity. J Neurol Neurosurg Psychiatry 2001;70(1):56–64.

4. Kijner RC, Fracchia SA, Abudussinina: a delayed-neuro-ophthalmic complication of cranial radiation. J Ophthalmol 2016:51(1):e157–8.

5. Kanai K, Kowabara S, Misawa S, Tamura N, Ogawara K, Nakata M, Sawai S, Hattori T, Bostock H. Altered axonal excitability properties in amyotrophic lateral sclerosis: impaired potassium channel function related to disease stage. Brain 2009;132(8):2531–41.

6. Kimura J, Taic M. An interspersed interval difference stochastic spike train analysis: detecting local trends in the temporal firing patterns of single neurons. Biolog Cybernetics 1999;80(5):309–26.

7. Forster FA, Alpers PM. Algiers of fasciculations in voluntary muscle. Arch. of biology 1944;51(3):264–7.

8. Freund B, Maddali M, Lloyd TE. A Case of Morvan Syndrome Mimicking Amyotrophic Lateral Scherosis With Fronto temporal Dementia. J Clin Neurosci 2000;7(4):207–11.

9. Frey D, Schneider C, Xu L, Borg J, Spooren W, Caroni P. Early and selective loss of neuromuscular synapse subtypes with low sprouting competence in motoneuron diseases. J Neurosci 2000;20(7):2534–42.

10. Frigo G, Grema P. A Study of SEMP in myokymia: a review and state-of-the-art. Clin Biomech (Bristol, Avon) 2009;24(3):236–45.

11. Fuller G. How to get the most out of nerve conduction studies and electromyography. J Neurol Neurosurg Psychiatry 2005;76(Suppl 2):i41–6.

12. Guthrie AR, Wiederkehr M, Meuli-Simmen C, Schweger G. Focal myokymia: do I love you? J Neurol 2010;257(10):1727–9.

13. Ginsburg G, Forde R, Martyn JA, Eikermann M. Increased sensitivity to a nondopaminergic muscle relaxant in a patient with acquired neuromyotonia. Muscle Nerve 2009;40(1):139–42.

14. Gonzalez Primomo SN, Blas L, Bertotti AC, Ameri C. Urinary manifestations in neuromyotonia: a delayed-neuro-ophthalmic complication of cranial radiation. J Ophthalmol 2016;51(1):e157–8.

15. Grandas F, Elston J, Quinn N, Marsden CD. Blepharospasm: a review of 264 patients. J Neurol Neurosurg Psychiatry 1988;51(6):767–72.

16. Graessle F, Elston J, Quinn N, Marsden CD. Blepharospasm: a review of 264 patients. J Neurol Neurosurg Psychiatry 1988;51(6):767–72.

17. Gray DF, Tavol H, Hahn AF, Barohn R, Salagejheh MG, Griggs RC, Bundy BN, Jen JC, Baloh RW, Hanna MG. Episodic ataxia type 1: clinical characterization, quality of life and genotype–phenotype correlation. Brain 2014;137(4):1009–18.

18. Grimm A, Prell T, Décard BF, Schumacher U, Witte OX, Auer H, Grosskreutz J. Fibrillation potentials and positive sharp waves: are they the same? Electroencephalogr Clin Neurophysiol 1991;81(3):163–6.

19. Gunther AM, Wiederkehr M, Meuli-Simmen C, Schweger G. Focal myokymia: do I love you? J Neurol 2010;257(10):1727–9.

20. Hansel D, Guleke B, Gungor H, Uyyal O, Sh J. Fluorinized-induced fasciculation-myokymia. J Clin Neurosci 2011;18(12):246–7.

21. Kiernan MC, Hart I. The instability properties of motor axons in patients with spontaneous motor unit activity. J Neurol Neurosurg Psychiatry 2001;70(1):56–64.

22. Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, Burrell JR, Zoing MC. Amyotrophic lateral sclerosis: a review of 264 patients. J Neurol Neurosurg Psychiatry 2011;82(4):384–8.

23. Kijfyz A, Emkecki B, Gungor H, Uyyal O, Sh J. Fluorinized-induced fasciculation-myokymia. J Clin Neurosci 2011;18(12):246–7.

24. Kleine BU, Stegeman DF, Hart I. The instability properties of motor axons in patients with spontaneous motor unit activity. J Neurol Neurosurg Psychiatry 2001;70(1):56–64.

25. Kijner RC, Fracchia SA, Abudussinina: a delayed-neuro-ophthalmic complication of cranial radiation. J Ophthalmol 2016:51(1):e157–8.

26. Kanai K, Kowabara S, Misawa S, Tamura N, Ogawara K, Nakata M, Sawai S, Hattori T, Bostock H. Altered axonal excitability properties in amyotrophic lateral sclerosis: impaired potassium channel function related to disease stage. Brain 2009;132(8):2531–41.

27. Katjuri B. Peripheral nerve hyperexcitability. Handb Clin Neurol 2019;161:281–90.

28. Katrak SM, Pollock M, Brien CPO, Nukada H, Allpress S, Calder C, Palmer DG, Greenman DM, McCormack FD. Autonomic, clinical and morphological features of gold neuropathy. Brain 1980;103(3):671–93.

29. Khindas S, Fraser JA. Abducens neuromyotonia: a delayed-neuro-ophthalmic complication of cranial radiation. J Ophthalmol 2016;51(1):e157–8.

30. Kijfyz A, Emkecki B, Gungor H, Uyyal O, Sh J. Fluorinized-induced fasciculation-myokymia. J Clin Neurosci 2011;18(12):246–7.

31. Kleine BU, Stegeman DF, Hart I. The instability properties of motor axons in patients with spontaneous motor unit activity. J Neurol Neurosurg Psychiatry 2001;70(1):56–64.

32. Kijner RC, Fracchia SA, Abudussinina: a delayed-neuro-ophthalmic complication of cranial radiation. J Ophthalmol 2016:51(1):e157–8.

33. Kanai K, Kowabara S, Misawa S, Tamura N, Ogawara K, Nakata M, Sawai S, Hattori T, Bostock H. Altered axonal excitability properties in amyotrophic lateral sclerosis: impaired potassium channel function related to disease stage. Brain 2009;132(8):2531–41.

34. Katjuri B. Peripheral nerve hyperexcitability. Handb Clin Neurol 2019;161:281–90.

35. Katrak SM, Pollock M, Brien CPO, Nukada H, Allpress S, Calder C, Palmer DG, Greenman DM, McCormack FD. Autonomic, clinical and morphological features of gold neuropathy. Brain 1980;103(3):671–93.

36. Khindas S, Fraser JA. Abducens neuromyotonia: a delayed-neuro-ophthalmic complication of cranial radiation. J Ophthalmol 2016;51(1):e157–8.
