MJD FOUNDATION

MEDICAL PROTOCOLS

Mobility and Balance Deterioration

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1. Background – Mobility and Balance Deterioration and MJD

The onset of mobility and balance difficulties occurs in the early stages of Machado Joseph Disease (MJD) progression. This mobility and balance difficulty manifests mostly as ataxia and a loss of coordination. Ataxia is a general term referring to the lack of muscle control or coordination, problems with fine motor control and posture. Together with visual disturbances (and consequently more pronounced ataxia in poor light), these are early clinical indicators that people may have MJD (in the absence of genetic testing). Friedman, D'Abreu and Jankovic (online) report that the loss of ankle reflex is a common feature early in the disease, but may appear in isolation and, thus, this sign in isolation is not helpful diagnostically.

The clinical manifestations of MJD can be highly variable, even among affected persons of the same family. One cause of this variability is the presence of different CAG repeat lengths within the MJD gene (ataxin-3) on chromosome 14q. Whilst the normal MJD gene can contain as many as 12-43 CAG repeats in a row, this repeat region is expanded in MJD patients to contain up to 86 CAG repeats (Gould, 2012). It is typically found that the longer the expansion length the more severe the disease. Mobility and balance deterioration, particularly gait ataxia, is associated with CAG length and age of symptom onset (Jardim et al., 2010; Klockgether et al., 1998).

People often report tripping or stumbling at night, and are seen to adopt a wide base of support with a staggering, ataxic or "drunken" walk. They reach for objects (e.g. furniture or another person) or walls with which to stabilise themselves, or avoid night activities all together. Difficulty ambulating through sand and/or over uneven terrain also becomes apparent. As the disease progresses, the musculoskeletal and vestibular systems deteriorate, causing individuals with the disease to experience a loss of muscle coordination, strength and endurance, slowness of movement, spasticity and rigidity, ultimately requiring the use of gait and balance aids through to wheelchair dependence.

The impact of MJD on the musculoskeletal and vestibular systems is largely a result of the disease targeting the cerebellum (National Institute of Neurological Disorders and Stroke, 2010). However, degeneration to other areas, including the brainstem, basal ganglia, the frontal, parietal, temporal, occipital and limbic lobes, spinal cord and thalamus have also been revealed on autopsy of MJD affected brains (D'Abreu et al., 2010; 2011; National Institute of Neurological Disorders and Stroke, 2010; Yamada et al., 2001). In MJD the rate of atrophy progression in the cerebellum and other regions is likely to be dependent on the CAG length and patient's age (Abe et al., 1998; Onodera et al., 1998).

1.1 Cerebellum

The cerebellum, located at the base of the brain, coordinates motor control and gait, balance, equilibrium and muscle tone (Centre for Neuro Skills, 2010). The cerebellum itself does not initiate movement but is required for the coordination and accuracy of movement. The cerebellum receives major inputs from the brainstem nuclei and the spinal cord and the cerebellum projects principally to the brainstem nuclei and thalamus. It also has strong

connections with the vestibular nuclei (nystagmus) and ventral lateral nucleus of the thalamus (motor control) (Bonthius, 2011).

Damage to the cerebellum can lead to:

1. Loss of coordination of motor movement (asynergia)
2. The inability to judge distance and when to stop (dysmetria)
3. The inability to perform rapid alternating movements (adiadochokinesia)
4. Movement tremors (intention tremor) – *See MJD Tremor/Spasticity Protocol*
5. Staggering, wide based walking (ataxic gait)
6. Tendency toward falling
7. Weak muscles (hypotonia) – *See MJD Muscle Weakness Protocol*
8. Slurred speech (ataxic dysarthria) – *See MJD Communication Difficulty Protocol* and
9. Abnormal eye movements (nystagmus) – *See MJD Vision Disturbance Protocol*.

(extracted from Centre for Neuro Skills, 2010)

1.2 Vestibular system

The vestibular system provides orientation in three dimensional space, modification of muscle tone and balance and it is essential for the coordination of motor responses, eye movement and posture. To maintain balance and body posture, there has to be a continuous flow of information to the system (Tascioglu, 2005).

Components of the midline zone of the cerebellum and the closely interconnected nuclei of the vestibular complex are responsible for postural mechanisms (gait, stance and trunk stability) (Rüb et al., 2004; Tascioglu, 2005).

A study by Rüb et al. (2004) on the degeneration of the central vestibular system in four MJD patients found that all five nuclei of the vestibular complex (interstitial, lateral, medial, spinal and superior nuclei) were vulnerable to the degenerative process in MJD and all three associated tracts (ascending tract of Deiters, juxtarestiform body, lateral and medial vestibulospinal tracts, medial longitudinal fascicle, vestibular portion of the eighth cranial nerve) underwent atrophy and demyelination. They concluded that this explains the truncal and postural instability and repeated falls that MJD patient's experience.

The extent of the neurodegeneration did not significantly correlate with the age at disease onset, age at death, the duration of the disease or CAG repeat length (all P-values > 0.5). They also conclude that the degeneration of the five nuclei occurs at different times and/or rates of the disease (Rüb et al., 2004).

1.3 Gait

Gait, or locomotion, is controlled by an elaborate circuitry involving the motor cortex, premotor cortex, caudate nuclei, cerebellum and spinal cord. In MJD neurons within many of these regions undergo neurodegeneration leading to multiple gait disturbances, e.g. loss of coordination and balance (degeneration of neurons within the cerebellum), trouble initiating movement (basal ganglia) and spasms (brainstem and spinal nuclei).

Gait ataxia is the most common neurological feature of MJD and is the first reported symptom in over 92% of MJD patients (Bettencourt and Lima, 2011). In most patients, the jerky quality/peculiar lurching type gait (a combination of cerebella ataxia and spasticity) distinguishes it from pure cerebellar ataxia gait (Friedman et al., online). Progression to dependence, due to loss of ambulation, while highly variable between individuals, generally occurs over 5 to 10 years (Sudarsky et al., 1992) and most people are wheelchair bound and fully dependent for activities of daily living within 10 to 15 years of the first symptoms emerging.

A study by Jardim et al. (2010) found that gait ataxia rate of progression is more clearly influenced by CAG expanded repeats and age onset[1] than other features such as limb ataxia, dystharia and dystonic movements. Females have been shown to have an increased risk of faster progression to loss of independence; however, gender does not influence survival times (Jardim et al., 2010; Klockgether et al., 1998).

Scale for the Assessment and Rating of Ataxia (SARA) scores are mainly determined by disease duration, age of disease onset and CAG length. Higher SARA scores also increased the risk of non-ataxia symptoms (D'Abrue et al., 2010).

[1] The length of repeat expansion accounts for 50-60 per cent of the variability in age of disease onset (D'Abreu et al., 2010)

2. Recommended Guidelines for addressing Mobility and Balance Deterioration in MJD Patients

It is recommended that individuals with MJD have regular (annual) neurological assessments (using the Scale for the Assessment and Rating of Ataxia) to provide an indication of baseline function and the annual progression rate of the disease. This data may also allow some objective measurement of the efficacy of recommended pharmaceutical and non-pharmaceutical treatments. It is important that MJD patients are reviewed annually, at a minimum, to address any progression in symptoms or address the emergence of new symptoms.

Appropriate qualified medical professionals should:

1. Conduct neurological assessment using SARA – see *Neurological Assessments per stage of disease DVD (https://vimeo.com/100856108)*
2. Conduct allied health assessments
    a. Prescribe any mobility aids and/or supportive footwear
    b. Refer to relevant specialists such as an occupational therapist or physiotherapist to develop an individual exercise program.
    c. Malnutrition Universal Screening Tool (MUST)
3. Discuss potential pharmaceutical options and prescribe, if appropriate.
4. Assess the patient's domicile and install suitable home modifications such as ramps, wheelchair accessible bathrooms, handrails, grab rails etc., to improve mobility and promote safety. (See MJD Assistive Technology Protocol)

3. Pharmaceutical Treatment options

Several pharmaceutical treatments have shown positive results for alleviating ataxia more generally; however, there are minimal large randomised control trials on the pharmaceutical options and the majority do not include or focus on MJD patients. Those promising pharmaceutical treatments (usually open label studies) have only been found to be effective on people with mild ataxia where the cerebellar cortexes are still relatively preserved.

Most of the medications aimed at improving mobility, balance and co-ordination in patients with ataxia mimic the neurotransmitters involved in motor control. These include pharmaceuticals that mimic glutamate and dopamine, in order to aid initiation and maintenance of movement, or mimic inhibitory neurotransmitters such as GABA, to dampen the excessive neural activity that causes spasms. Other drugs are targeted at hypothesised causes of neurodegeneration such as accumulation of mutant ataxin-3 protein and glutamate excitotoxicity (neuronal death due to excessive glutamate levels).

The following pharmaceutical treatments are a guide only and the individual circumstances of the patient must be considered.

3.1 Prescription pharmaceuticals

Amantadine (Symmetrel or mantadine) was one of the first drugs reported to improve movement and gait in MJD patients (100mg twice per day; Woods and Schaumburg, 1972). It has been tested in clinical trials for the treatment of ataxia (Friedreich's ataxia, followed by general heterogeneous ataxia, Peterson et al., 1988; Botez et al., 1996), but not specifically MJD. Amantadine acts as a NMDA receptor antagonist, thus preventing NMDA receptor mediated glutamate excitotoxicity, and also stimulates dopamine release. Botez et al. (1996), reported a mean improvement in upper limb motor co-ordination of 35% in patients with ataxia (including patients with SCA-1 and 2) treated with amantadine (200mg/day; n=15) compared to placebo (n=15).

Buspirone has been effective in treating mild to moderate cerebellar ataxia features (Lou et al., 1995; Trouillas et al., 2011); however, the effect is 'partial and not major'. Trouillas et al. (2011) found that patients receiving Buspirone (mean full dose was 69mg/day) had significantly greater improvements in the intensity of body sway ($p=0.009$) and the quality of standing with feet together ($p=0.01$). Baer et al. (2000), found in their study of 10 patients that even 20mg/day of buspirone is poorly tolerated by patients due to side effects of dizziness, increased imbalance and tremor. A non-Indigenous Australian with MJD is anecdotally self-reporting improvements in balance with Buspirone (10 mg in morning and 5 mg at night).

A recent randomized trial of 20 MJD patients found that 1mg of **verenicline** (Chantix/ Champix – a smoking cessation drug) over a four-week period significantly improved gait ($p=0.04$), stance ($p=0.03$), rapid alternating movements ($p=0.003$) and timed 25-foot walk ($p=0.05$). Overall, there was a trend towards improvement in SARA scores ($p=0.06$) (Zesiewicz et al., 2012).

Researchers are starting to recognise that the serotonin system may play a role in cerebellar dysfunction (Ogawa, 2004) and several studies have found benefits using **5-HT1A agonists** (serotonergic drugs) for the treatment of MJD (Liu et al., 2005; Lou et al., 1995; Takei et al., 2010; Trouillas et al., 2011). **Tandopirone** (15mg/day) was found effective in reducing patients' with mild MJD total scores on international cooperative ataxia rating scale (ARS) ($p=0.005$) and total length travelled (TLT) of body stabilometry ($p=0.002$). Of the fourteen MJD patients who participated in this study, four showed a greater than five point reduction in ARS and eight showed more than a ten per cent reduction in TLT (Takei et al., 2010). The authors previously found that 20mg per day resulted in some patients' ataxia deteriorating further (Takei et al., 2004).

Liu et al. (2005) have investigated the clinical effect of treatment with **lamotrigine** (25 mg twice a day) on six MJD patients with early truncal ataxia. Lamotrigine (LTG) effectively improved gait balance in the single leg standing test and tandem gait index scores in a study of 6 MJD patients. Lamotrigine is currently used as an anti-epileptic drug because of its action as a sodium channel blocker. It is hypothesised that it's benefits for MJD may stem from its indirect effect of decreasing glutamate induced excitotoxicity but Liu et al. (2005) have also reported that lamotrigine decreases expression of mutant ataxin-3 in cultured cells. Doctors prescribing LTG must be aware that LTG dosage should be kept low because higher dosages of LTG can in fact induce heightened ataxia and immobility, likely due to depleted glutamate levels. In addition, dangerous (sometimes fatal) skin allergies and hypersensitivities LTG can occur in some patients and must be monitored for in the first weeks of usage.

Ogawa et al. (2003) trialled the use of **D-Cycloserine**, a NMDA receptor agonist, for the treatment of ataxia symptoms. A 14-day single-blind trial of 50mg of D-Cycloserine (25mg at 08:00 hours and 25mg at 20:00 hours) in 15 MJD patients found that patients had significantly lower values ($p>0.05$) for the total score of international cooperative ataxia rating scale, posture, gait, timed test walking and pronouncing (Ogawa et al., 2003).

Studies have ruled out, due to lack of effectiveness and/or side effects, the following pharmaceutical treatments: tremthoprim-sulfamethoxazole (Schulte et al., 2001), fluoxetine (Monte et al., 2003) and quinine derivatives (Katzberg, Khan and So, 2010).

3.2 Non-prescription pharmaceuticals

Clients of the MJD Foundation have been anecdotally reporting that taking 1-2 chelated magnesium tablet/s per day (up to 1,000mg per day) reduces muscle cramping and spasms, and aids their mobility and balance. However, due to the lack of supporting evidence a subcommittee of the American Academy of Neurology concludes that the use of magnesium preparations and gabapentin are probably not effective in the treatment of muscle cramps (Katzberg, Khan and So, 2010).

One trial concluded that while magnesium was not effective for the treatment of nocturnal leg cramps, there may be a real placebo effect – all patients regardless of treatment (magnesium or placebo) improved over time (Frusso et al., 1999).

4. Therapeutic Treatment Options

Conservative approaches to managing mobility and balance symptoms include: supportive footwear to promote good foot position; Ankle-Foot Orthoses (AFOs) to maintain optimal musculoskeletal integrity of the lower leg; physical and balance exercises (incorporating active and passive joint range of motion, muscle stretching, functional strength and balance exercises)

4.1 Ankle-Foot Orthoses (AFOs)

AFOs could be useful as client's dorsiflexion becomes weaker and the resultant foot-drop and/or ankle instability is contributing to trips and/or falls. AFOs will provide most benefit in the early stages of mobility/ balance deterioration i.e. when stumbling and tripping are first noticed. Caution in prescribing AFOs for MJD clients who live in humid or hot climates must be observed, as they may experience sweating, discomfort and skin breakdowns.

It is recommended that MJD clients be fitted for customised AFOs (and indeed any splints or prostheses they may be recommended) rather than "off the shelf" items, and they must be continually monitored for correct fit. As MJD progresses, people can experience rapid weight loss (they become malnourished as a result of their dysphagia), and also lose muscle mass as their functional status declines.

Refer to the Difficulty Swallowing Medical Protocol and the Nutrition Medical Protocol for further information on dysphagia and malnutrition.

4.2 Exercise and balance program

As per any population group, regular physical activity to promote cardiovascular health and endurance is always recommended (however, consideration must be made for fatigue, environmental conditions and/or exacerbation of symptoms).

D'Abrue et al. conclude that exercise programs may be beneficial for MJD patients' physical functions, health related quality of life, balance, strength and gait (similar to the benefits found in Parkinson's Disease patients). Without further studies they can not conclude it will slow the progression of the disease; however they believe 'it helps patients cope with their disabilities … [and] increase self-esteem and boosts patients' mood and sense of control over their disease' (2010, pp. 5).

A study looking at a mouse model of spinocerebellar ataxia type 1 (Fryer et al., 2011) found that a mild exercise regimen provided long lasting effect on life span (however, no significant improvements in motor performance). Authors suggest that individuals with SCA1 'might benefit from an exercise program early in disease course' and a more intense or longer-duration exercise could lead to motor improvements (Fryer et al., 2011).

Specific balance exercises, with and without vision occluded in the mild and moderate stages, and functional balance activities (i.e. walking over uneven terrain) may assist people to slow the progression of ataxia. The Otago Exercise Programme, a balance and strength focused individually tailored program, has been shown to successfully reduce falls in at risk groups

(particularly in the elderly). The program consists of a set of leg muscle strengthening and balance retraining exercises (progressing in difficulty) and a walking plan. Ankle cuff weights are also used to provide resistance for the strengthening exercises (Campbell and Robertson, 2003).

Four control trials found that the program (when delivered to older people) reduced falls and injuries from falls by 35% (Campbell and Robertson, 2003).

Individually or group prescribed Otago Exercise Programmes may be beneficial to MJD patients; however, no formal studies involving participants with MJD are known.

5. Other Treatment Options

Several mobility aids such as canes, walkers or wheelchairs, can assist MJD patients to live more independently for longer and reduce the number of falls. As the disease progresses, different assistive devices will be necessary and therefore clinicians must perform regular SARA reviews and physical examinations. It is important to remember that each person with MJD experiences it differently, and his or her needs, including their home and community environment, must be taken into account.

Refer to Assistive Technologies (Equipment) per stage of Disease Medical Protocol for a comprehensive list of mobility devices.

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Appendix B – Definitions

Adiadochokinesia: the inability to perform rapid alternating movements

Asynergia: loss of coordination of motor movement

Ataxia: is the 'absence of order'. People with ataxia have problems with coordination of muscle movements due to the dysfunction of the nervous system, including damage to the cerebellum.

Ataxic Dysarthria: slurred speech

Ataxic gait: staggering, wide based walking

CAG: a codon in mRNA for L-glutamine. MJD is the result of a CAG-repeat or polyglutamine disease characterised by expansions of (CAGn) trinulceotide repeat sequences (Rüb et al., 2004).

Dorsiflexion: the movement which decreases the angle between the dorsum (superior surface) of the foot and the leg, so that the toes are brought closer to the shin

Dysmetria: the inability to judge distance and when to stop

Hypotonia: weak muscles

Nystagmus: abnormal eye movements

SARA: Scale for the Assessment and Rating of Ataxia (SARA) is an 8-item international tool to rate the severity of an individual's ataxia. Studies have found that SARA is a reliable and valid measure of ataxia (Schmitz-Hubsch et al., 2006).

Vestibular Complex: The vestibular nuclei lie in the lateral recess of the rhomboid fossa extending from a level rostral to the hypoglossal nucleus slightly above the abducens nucleus. Five nuclei are important in MJD patients - interstitial, lateral, medial, spinal and superior nuclei. (Rüb et al., 2004; Tascioglu, 2005).

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