Clinical Management Guidelines for Friedreich Ataxia

Chapter 6. Pulmonary function and sleep disturbance in Friedreich ataxia

Contents

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Funding

The authors of this document gratefully acknowledge the support of the Friedreich Ataxia Research Alliance (**FARA)**. The views and opinions expressed in the Guidelines are solely those of the authors and do not necessarily reflect the official policy or position of FARA.

6. Pulmonary function and sleep disturbance in Friedreich ataxia

This chapter describes the effects of Friedreich ataxia on pulmonary function and sleep disturbance, including sleep disturbance related to breathing problems and that related to restless legs or periodic limb movements. It also covers strategies for monitoring pulmonary function and managing reduced pulmonary function and sleep disturbance. In making recommendations for management of reduced pulmonary function and sleep disturbance, the authors were tasked with answering the following questions:

For individuals with Friedreich ataxia, what management strategies could be implemented for reduced pulmonary function and preventing pulmonary infections? (see 6.1)

For individuals with Friedreich ataxia, what management strategies could be implemented for breathing related sleep disturbance? (see 6.2)

For individuals with Friedreich ataxia, what management strategies could be implemented for restless legs and/or sleep related periodic limb movements? (see 6.3)

6.1 Reduced pulmonary function and pulmonary infection

Sub Subramony and Katherine Mathews

6.1.1 The effects of Friedreich ataxia on pulmonary function

There are no large-scale published data on pulmonary function tests in Friedreich ataxia (FRDA). Bulbar dysfunction and muscle weakness (related to upper motor neuron pathology) do occur in FRDA and may lead to restrictive lung disease. Neuromuscular restrictive lung disease typically leads to nocturnal hypoventilation causing sleep disturbance and abnormal nocturnal blood gases, with deleterious effects. Nocturnal problems may be compounded by the occurrence of obstructive sleep apnea. In a small unpublished observational study, close to 20% of participants with FRDA had one or more abnormal pulmonary function test (PFT) values, usually in those with more advanced FRDA (Corti, Smith & Subramony, unpublished data).

Other neuromuscular disorders such as Duchenne muscular dystrophy and amyotrophic lateral sclerosis, in which some data exist and care guidelines have been developed, are not strictly comparable due to greater degree of muscle strength loss in these illnesses; nevertheless, these can serve as models for the care of individuals with FRDA (1-4).

6.1.2 Monitoring pulmonary function

Monitoring for reduced pulmonary function should be done at least annually in Individuals with FRDA with advanced disease (i.e., non-ambulatory; or earlier if symptoms of sleep disordered breathing are elicited) during clinic visits.

Monitoring at clinic visits should include the following:

- Administer a neuro-respiratory checklist including questions about orthopnea, dyspnea during ordinary daytime activities, apnea during the night, poor sleep quality during the night, morning headache, decreased attention and concentration during the daytime, excess daytime sleepiness, excessive fatigue and repeated chest infections (5)
- Administer a sleepiness questionnaire (e.g., Epworth sleepiness scale) and a fatigue scale
- Assess respiratory excursions and cough strength during physical examination

- In individuals with advanced FRDA, perform tests for different respiratory muscle groups at least annually, including:
    - Spirometry: measure forced vital capacity (FVC) sitting and supine. A significant decline in supine FVC reflects diaphragmatic dysfunction
    - Other PFT measures such as lung volumes and maximal respiratory pressures
    - Peak expiratory cough flow (PECF)
    - Pulse oximetry and end tidal CO_2 or transcutaneous pCO_2
- Polysomnography with capnography if obstructive sleep apnea or nocturnal hypoventilation is suspected based on above clinic based assessments.

6.1.3 Management of reduced pulmonary function and preventing pulmonary infection

- Consider chest physiotherapy and respiratory strength training. This may be more useful in the event of an acute intervening medical issue such as lung infection or surgery.
- For help with airway clearance, manual assisted coughing or mechanical insufflation-exsufflation (MI-E) is recommended if FVC < 50% predicted or PECF < 270 L/min or when maximum expiratory pressure is < 60 cm H_2O. Individual titration of MI-E is recommended.
- Initiate nocturnal assisted non-invasive ventilation (NIV) if any of the following indications exist: FVC < 50% predicted; maximum inspiratory pressure < 60 cm H_2O; nocturnal hypercarbia (pCO_2 > 50 mm Hg for ≥ 2% of sleep time or a 10 mm Hg increase in pCO_2 compared to awake baseline pCO_2 for ≥ 2% of sleep time); nocturnal hypoxia (SpO_2 ≤ 88% for ≥ 2% of sleep time or 5 minutes continuously); or apnea-hypopnea index ≥ 5. Daytime hypoventilation indicated by hypercarbia of > 45 mm Hg or baseline PO_2 < 95% on room air is also an indication for nocturnal assisted ventilation.
- Individuals with advanced FRDA and their caregivers should be educated regarding the risk of respiratory complications including higher risk of severe infections and the role of impaired airway clearance.
- Risk of pneumonia can be reduced for those with more severe FRDA through appropriate vaccinations for bacterial and viral infections (such as pneumovax and annual flu vaccines) and “social distancing” strategies when in contact with others.

Best practice statement

Individuals with advanced Friedreich ataxia should be monitored for reduced pulmonary muscle strength and restrictive lung disease. Based on data from clinical evaluations, pulmonary function testing and possibly sleep studies, interventions such as assisted airway clearance techniques and non-invasive assisted ventilation should be offered.

Recommendations

Grading for strength of recommendation and level of evidence

For the rating of the **strength** of the recommendation, in addition to evidence from studies in FRDA, evidence from like conditions, clinical experience and expert consensus are taken into account when published evidence is not available.

The **level of evidence** is based on published evidence from studies in FRDA. If there is no published evidence in FRDA, evidence from other like conditions or clinical expertise may have been used to

make the recommendation – this is graded as 'very low' or in some cases 'low' level evidence. See the table below for an explanation of the symbols used to grade recommendations.

Strength of recommendation	Symbol	Level of evidence	Symbol
Strong for intervention	↑↑	High	⊕⊕⊕⊕
Conditional for intervention	↑	Moderate	⊕⊕⊕◯
Neither intervention nor comparison	—	Low	⊕⊕◯◯
Conditional against intervention	↓	Very low	⊕◯◯◯
Strong against intervention	↓↓		

Monitoring

Should monitoring for restrictive lung disease/sleep disordered breathing/sleep apnea versus no monitoring be used for people with Friedreich ataxia?	**Strength**	**Level of evidence**
We conditionally recommend that individuals with advanced Friedreich ataxia be monitored* at least annually for restrictive lung disease and sleep disordered breathing (SDB). *Monitoring should include a respiratory symptom check list (dyspnea, orthopnea, episodes of apnea during night, poor sleep, morning headache, decreased concentration and attention, fatigue, treated chest infection within the past few months), a sleepiness questionnaire and a fatigue scale. Annual (or more frequent) pulmonary function testing should be performed to include forced vital capacity (FVC), maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP), peak expiratory cough flow (PECF), SpO_2 and partial pressure of end tidal CO_2 ($PetCO_2$).	↑	⊕◯◯◯
Justification: There are no published data. Expert opinion and limited unpublished data suggest that restrictive lung disease and SDB can occur in advanced Friedreich ataxia. Monitoring will be of benefit. Methods for monitoring include using a respiratory symptom check list (5), sleepiness and fatigue scales and pulmonary function tests. Restrictive lung disease and SDB can lead to abnormal blood gases and symptoms that impair quality of life. Detecting these and providing appropriate intervention will be of benefit.		
Subgroup considerations: Monitoring is recommended for individuals with Friedreich ataxia with advanced disease.		

Monitoring at diagnosis

Should monitoring for restrictive lung disease/sleep disordered breathing/sleep apnea at diagnosis versus monitoring at later stages be used for people with Friedreich ataxia?	**Strength**	**Level of evidence**

We conditionally recommend *against* monitoring for restrictive lung disease and sleep disordered breathing at diagnosis of Friedreich ataxia rather than at later stages of the disease, as there is no evidence that this would be of benefit.	↓	⊕◯◯◯
Justification: There are no published data on prevalence of abnormal respiratory muscle function in Friedreich ataxia. Unpublished data indicates that restrictive lung disease and impaired cough can occur in later stages of the disease. There is no clear evidence of the effect of monitoring for restrictive lung disease/SDB/sleep apnea at diagnosis compared to later in the disease, on abnormal lung volumes; impaired airway clearance; excessive daytime sleepiness, or fatigue in individuals with Friedreich ataxia. Monitoring could be done in later stages of Friedreich ataxia.		
Subgroup considerations: Individuals who are later in the progression of Friedreich ataxia are more likely to experience restrictive lung disease.		

Assisted coughing

Should assisted coughing (mechanical/manual) versus no intervention be used for impaired airway clearance in Friedreich ataxia?	**Strength**	**Level of evidence**
In individuals with Friedreich ataxia and impaired airway clearance (PECF < 270 L/min or FVC < 50% predicted), we suggest assisted coughing (mechanical/manual) be implemented to assist in airway clearance and reduce the prevalence of chest infections.	↑	⊕◯◯◯
Justification: Poor cough mechanisms likely occur in some individuals with advanced Friedreich ataxia. There are no major studies that address assisted coughing interventions in Friedreich ataxia. A patient survey suggests that this is an important problem and Friedreich ataxia experts seem to agree. One of the authors has unpublished data indicating impaired cough flow occurs in advanced Friedreich ataxia. It may be conjectured that improved clearance of secretions will likely reduce probability of chest infections. Chest infection is second to cardiac disease as a cause of mortality in Friedreich ataxia (6).		
Subgroup considerations: This intervention should be considered for individuals with Friedreich ataxia who are non-ambulatory and have impaired cough flow and/or reduced forced vital capacity.		

Chest physiotherapy

Should chest physiotherapy versus no intervention be used for people with respiratory weakness and restrictive lung disease with Friedreich ataxia?	**Strength**	**Level of evidence**
In people with respiratory weakness and restrictive lung disease with Friedreich ataxia, we conditionally recommend chest physiotherapy to improve respiratory function, reduce prevalence of chest infection, reduce dyspnea and improve airway clearance function.	↑	⊕◯◯◯
Justification: There are no published data on restrictive lung disease and interventions in Friedreich ataxia. A patient survey and unpublished data from one of the authors indicate that this		

occurs in some patients with advanced Friedreich ataxia. A survey of experts suggests that chest physiotherapy provides benefit for respiratory function, chest infections, and airway clearance.
Subgroup considerations: This recommendation is for people with Friedreich ataxia with respiratory weakness and restrictive lung disease. Chest physiotherapy may be particularly useful in the event of an acute superimposed medical issue such as surgery or chest infection.

Non-invasive assisted ventilation

Should non-invasive ventilation versus no intervention be used for restrictive lung disease in Friedreich ataxia?	**Strength**	**Level of evidence**
We conditionally recommend non-invasive assisted ventilation for patients with Friedreich ataxia and documented restrictive lung disease meeting the following thresholds: FVC < 50% predicted; maximum inspiratory pressure < 60 cm H_2O; nocturnal hypercarbia (pCO_2 > 50 mm Hg for ≥ 2% of sleep time or a 10 mm Hg increase in pCO_2 compared to awake baseline pCO_2 for ≥ 2% of sleep time); nocturnal hypoxia (SpO_2 ≤ 88% for ≥ 2% of sleep time or 5 minutes continuously); or apnea-hypopnea index ≥ 5. Daytime hypoventilation indicated by hypercarbia of > 45 mm Hg or baseline PO_2 < 95% on room air is also an indication for nocturnal assisted ventilation.	↑	⊕◯◯◯
Justification: Restrictive lung disease can lead to abnormal blood gases with deleterious effects on cardiopulmonary health and also lead to symptoms that impair quality of life, both during the daytime and during sleep. There is no data on the use of non-invasive assisted ventilation in patients with Friedreich ataxia. This recommendation is based on limited data from similar disorders and expert guidelines in such disorders.		
Subgroup considerations: This recommendation is for individuals with advanced Friedreich ataxia and abnormal pulmonary function.		

Respiratory strength training

Should respiratory strength training versus no intervention be used for people with respiratory weakness and restrictive lung disease with Friedreich ataxia?	**Strength**	**Level of evidence**
We cannot recommend either respiratory strength training or no respiratory strength training for people with Friedreich ataxia and respiratory weakness and restrictive lung disease. We suggest that in selected patients with respiratory weakness, supervised respiratory training be considered with monitoring of respiratory parameters and for adverse effects such as exhaustion.	—	⊕◯◯◯
Justification: Respiratory weakness can lead to symptoms of sleep disordered breathing such as fatigue, excessive daytime sleepiness and dyspnea and nocturnal abnormalities in blood gases with deleterious effects. However, there are no published data regarding monitoring methods or respiratory strength training in Friedreich ataxia. Based on limited low-level evidence in small studies and meta-analysis in some similar disorders, there is little objective evidence for respiratory strength training as an intervention for respiratory weakness (7, 8). However, Friedreich ataxia expert opinion suggests that respiratory strength training may be considered for		

individuals with later stage Friedreich ataxia with impaired pulmonary function tests indicating respiratory weakness.
Subgroup considerations: This intervention could be considered for individuals with later stage Friedreich ataxia with impaired pulmonary function tests indicating respiratory weakness.

Lay summary

Lay summary of clinical recommendations for reduced pulmonary function & preventing pulmonary infection in Friedreich ataxia

Why these recommendations?

There are no good quality studies looking at the effects of Friedreich ataxia on breathing or possible treatments. However, the limited research available suggests that breathing problems can happen in patients who are in the later stages of the disease. Experience from other similar (but not identical) neuromuscular disorders suggests that although breathing changes may happen in Friedreich ataxia, breathing may be less affected than in the other disorders. This is due to muscle weakness not being as severe in Friedreich ataxia.

Weakness of breathing muscles may involve both the muscles that work to make air flow into the lungs (inspiratory muscles) and those that expel air from the lungs (expiratory muscles). Less capacity to pull air in can lead to “stiffening” of lung tissue and chest muscles (reduced compliance). This can lead to the collapse of the air pockets in the lungs (atelectasis), thereby making the problem worse. Spinal curvature (common in Friedreich ataxia) can also affect breathing function.

Impaired breathing can lead to reduction in oxygen levels in blood and tissues (oxygen desaturation) and increases in carbon dioxide levels (hypercarbia), both of which may cause problems and symptoms: these include poor sleep and daytime sleepiness, headache, fatigue and shortness of breath. If expiratory muscles are weakened, coughing is less effective, and the ability to clear fluids from lungs is reduced. This can lead to lung infections.

We suggest that monitoring for breathing problems in individuals with Friedreich ataxia once they are not ambulatory could be helpful.

Monitoring may include:

- asking about daytime symptoms such as sleepiness, fatigue, headache in the morning, and episodes of chest infection since the last clinic visit
- paying attention to chest motion and cough effectiveness during a physical examination
- lung function tests, including tests to evaluate cough and to measure lung volumes. These should be done at least yearly, or when symptoms happen.
- Other tests that could be useful include measuring oxygen and carbon dioxide levels in the blood using non-invasive techniques.
- An overnight sleep study may also be useful in selected individuals to see if respiratory weakness causes problems during sleep.

If these tests point to the need, interventions may be recommended, including:

- assisted coughing methods
- use of devices such as biPAP or AVAPS to increase air entry into the lungs and normalize blood oxygen and carbon dioxide levels

- respiratory strength training.

Individuals with Friedreich ataxia and impaired lung function may find it difficult to tolerate some of these interventions.

Individuals with more severe Friedreich ataxia can exercise “respiratory infection prevention strategies”. These include vaccinations for bacterial and viral infections and “social distancing” strategies when in contact with others. This recommendation is based on the experience of Friedreich ataxia experts and limited data from other similar disorders, as there is little direct evidence for infection prevention strategies in Friedreich ataxia.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

It may be important for you to discuss possible difficulty with breathing with your care providers and encourage good communication between members of your care team, including your neurologist, pulmonary or sleep specialist, physical therapist and primary care physician.

Who are these recommendations specifically for?

These recommendations are relevant for individuals with Friedreich ataxia who have more advanced disease or are experiencing breathing and/or sleep problems.

6.2 Breathing related sleep disturbance and nocturnal hypoventilation

Sub Subramony, Barbara Smith, Katherine Mathews and Louise Corben

6.2.1 The effects of Friedreich ataxia on sleep disordered breathing

Sleep disordered breathing (SDB) has not been extensively documented in Friedreich ataxia (FRDA). There is a single case report documenting a patient with severe FRDA and “arduous” breathing and oxygen desaturation, together with SDB at night (9). Manni et al (10) reported polysomnography on nine persons with various hereditary ataxias and reported SDB in three people with FRDA. In a study from Australia, Corben et al (11) administered the Epworth Sleepiness Scale to 82 individuals with FRDA and found abnormal values in 21. Polysomnography in these selected individuals documented obstructive sleep apnea (OSA) in 17 of the 21. The risk of OSA in FRDA was estimated to be over 5 times that in the general population. In a web-based survey of FRDA individuals in the FARA registry (12), 16.4% reported a diagnosis of sleep apnea. Sleep apnea is associated with older age and/or longer duration of disease (11, 12).

SDB in neuromuscular disorders such as FRDA can result from different problems. Reduced muscle tone in the upper airway leads to OSA. Reduced respiratory muscle strength leading to reduced respiratory volumes and lessening chest wall compliance causing atelectasis and subsequent ventilation-perfusion mismatch can lead to nocturnal hypoventilation, even without sleep apnea, though this was not seen in the study from Australia (11). Both sleep apnea and nocturnal hypoventilation can lead to daytime symptoms that include excessive sleepiness, fatigue, poor concentration, morning headache, dyspnea and orthopnea.

6.2.2 Monitoring sleep disordered breathing

Monitoring for SDB should be done at least annually in individuals with FRDA with advanced disease (i.e., non-ambulatory; or earlier if symptoms of SDB are elicited) during clinic visits.

Monitoring at clinic visits should include:

- Administer a neuro-respiratory checklist including questions about orthopnea, dyspnea during ordinary daytime activities, apnea during the night, poor sleep quality during the night, morning headache, decreased attention and concentration during the daytime, excess daytime sleepiness, excessive fatigue and repeated chest infections (5)
- Administer a sleepiness questionnaire (e.g., Epworth sleepiness scale) and a fatigue scale
- Assess respiratory excursions and cough strength during physical examination
- Perform pulmonary function tests (PFT) to include forced vital capacity, maximal inspiratory and expiratory pressures and peak expiratory cough flow
- Polysomnography with capnography if obstructive sleep apnea or nocturnal hypoventilation is suspected based on above clinic based assessments.

6.2.3 Management of sleep disordered breathing

- SDB primarily diagnosed as OSA can be managed with continuous positive airway pressure (CPAP) at night
- While CPAP is the primary treatment of OSA, alternative therapies may be used in certain situations. For a clear nasopharyngeal obstruction, nasal steroids or removal of obstruction may be indicated. Individuals with mild OSA may be prescribed a customized oral appliance to support the position of the mandible and promote airway patency during sleep.
- Nocturnal hypoventilation is managed by non-invasive ventilation using bi-level positive airway pressure (biPAP) or average volume assured pressure support (AVAPS) (see section 6.1: Management of reduced pulmonary function)
- General health measures, such as maintaining ideal weight, sleep hygiene and avoidance of alcohol, should be recommended

To inform clinical practice, more data are needed on the prevalence of SDB in FRDA, the risk factors associated with it and the effects of interventions on symptom reduction, quality of life and on progression of cardiac and neurological manifestations of FRDA

Best practice statement

Individuals with advanced Friedreich ataxia should be monitored for sleep disordered breathing using clinical questionnaires and assessments. When obstructive sleep apnea is diagnosed, appropriate night-time ventilatory assistance or an appropriate alternative treatment should be offered.

Recommendations

Monitoring

Should monitoring for restrictive lung disease/sleep disordered breathing/sleep apnea versus no monitoring be used for people with Friedreich ataxia?	**Strength**	**Level of evidence**
We conditionally recommend that individuals with advanced Friedreich ataxia be monitored* at least annually for restrictive lung disease and sleep disordered breathing (SDB).	↑	⊕◯◯◯

*Monitoring should include a respiratory symptom check list (dyspnea, orthopnea, episodes of apnea during night, poor sleep, morning headache, decreased concentration and attention, fatigue, treated chest infection within the past few months), a sleepiness questionnaire and a fatigue scale. Annual (or more frequent) pulmonary function testing should be performed to include forced vital capacity (FVC), maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP), peak expiratory cough flow (PECF), SpO_2 and partial pressure of end tidal CO_2 ($PetCO_2$).		
Justification: There are no published data. Expert opinion and limited unpublished data suggest that restrictive lung disease and SDB can occur in advanced Friedreich ataxia. Monitoring will be of benefit. Methods for monitoring include using a respiratory symptom check list (5), sleepiness and fatigue scales and pulmonary function tests. Restrictive lung disease and SDB can lead to abnormal blood gases and symptoms that impair quality of life. Detecting these and providing appropriate intervention will be of benefit.		
Subgroup considerations: Monitoring is recommended for individuals with Friedreich ataxia with advanced disease.		

Monitoring at diagnosis

Should monitoring for restrictive lung disease/sleep disordered breathing/sleep apnea at diagnosis versus monitoring at later stages be used for people with Friedreich ataxia?	**Strength**	**Level of evidence**
We conditionally recommend *against* monitoring for restrictive lung disease and sleep disordered breathing at diagnosis of Friedreich ataxia rather than at later stages of the disease, as there is no evidence that this would be of benefit.	↓	⊕◯◯◯
Justification: There are no published data on prevalence of abnormal respiratory muscle function in Friedreich ataxia. Unpublished data indicates that restrictive lung disease and impaired cough can occur in later stages of the disease. There is no clear evidence of the effect of monitoring for restrictive lung disease/SDB/sleep apnea at diagnosis compared to later in the disease, on abnormal lung volumes; impaired airway clearance; excessive daytime sleepiness, or fatigue in individuals with Friedreich ataxia. Monitoring could be done in later stages of Friedreich ataxia.		
Subgroup considerations: Individuals who are later in the progression of Friedreich ataxia are more likely to experience restrictive lung disease.		

Non-invasive ventilation

Should non-invasive ventilation versus no intervention be used for sleep disordered breathing (SDB)/sleep apnea and nocturnal hypoventilation in Friedreich ataxia?	**Strength**	**Level of evidence**
In individuals with Friedreich ataxia and sleep disordered breathing/sleep apnea and/or evidence of nocturnal hypoventilation, we suggest non-invasive ventilation be implemented to assist in fatigue;	↑	⊕◯◯◯

sleepiness; quality of night time sleep; blood gas parameters; and cardiac function.		
Justification: Sleep apnea and nocturnal hypoventilation related to obstructive sleep apnea or restrictive lung disease cause abnormal blood gases and lead to symptoms with deleterious consequences. There are no published data in Friedreich ataxia on the use of non-invasive ventilation (NIV). Also, there are no recent publications on this in other neuromuscular disorders. A Cochrane review from 2014 (13) found low level evidence in favor of NIV for reducing mortality, reducing unexpected hospitalizations, and reducing symptoms of SDB and hypoventilation in other neuromuscular disorders (mostly ALS and DMD). Care recommendation guidelines in similar disorders include nocturnal assisted ventilation for SDB, sleep related hypoventilation and abnormal pulmonary function tests.		
Subgroup considerations: This recommendation is for individuals with advanced Friedreich ataxia with documented sleep disordered breathing including nocturnal hypoventilation and/or abnormal pulmonary function tests.		

Lay summary

Lay summary of clinical recommendations for breathing related sleep disturbance & nocturnal hypoventilation in Friedreich ataxia

Why these recommendations?

Limited research shows that sleep disruption due to sleep disordered breathing (SDB) happens in individuals with Friedreich ataxia, particularly those who are in the later stages of the disease. Experience from other neuromuscular disorders suggests that SDB can be related to problems with the muscles that control breathing and throat and upper airway muscles, as well as stiffening of the chest muscles and lungs. Sleep disruption can also be unrelated to breathing problems (such as disruption due to restless legs).

Disrupted sleep related to SDB includes sleep apnea (short periods when breathing stops during sleep), often from throat muscles closing off (obstructive sleep apnea), and nocturnal hypoventilation, where there is not enough movement of air into the lungs during sleep. Nocturnal hypoventilation results from weak respiratory muscles and can lead to high carbon dioxide and low oxygen levels in the blood. In other diseases, this often happens in those with shallow breath volumes, since the depth of breathing falls further during sleep. Sleep apnea and nocturnal hypoventilation must be considered in individuals with poor sleep quality and daytime fatigue and sleepiness, or in those with shallow breathing.

Monitoring for sleep disorders in individuals with Friedreich ataxia includes:

- asking about daytime sleepiness or fatigue, headache in the morning, snoring or shortness of breath
- a sleep study (polysomnography) for those reporting a history of snoring and poor sleep quality.
- Individuals who are no longer ambulatory are at increased risk for nocturnal hypoventilation and sleep apnea; it is recommended they undergo appropriate lung function tests at least yearly or if they experience concerning symptoms.
- Other tests might include measuring oxygen levels using a “pulse oximeter” attached to the finger, and carbon dioxide levels in air being expelled, usually done by placing a

cannula in the nostrils. Tests of oxygen and carbon dioxide levels in the blood can provide an indication of hypoventilation, as can a sleep study.

Treatments for sleep disordered breathing are generally targeted at the underlying problem:

- If the problem is failure to maintain an open airway at the level of the throat, continuous positive airway pressure (CPAP) provided through a mask can be helpful.
- If the problem is nocturnal hypoventilation, then treatment is focused on increasing the volume of the breaths taken in sleep using bilevel positive airway pressure (biPAP; provides supported breaths) or average volume assured pressure support (AVAPS) during sleep.
- There are other interventions that target anatomical obstructions in selected individuals with obstructive sleep apnea.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

It may be important for you to discuss possible problems with sleep with your care providers and encourage good communication between members of your care team, including your neurologist, pulmonary or sleep specialist, physical therapist and primary care physician.

Who are these recommendations specifically for?

These recommendations are relevant for individuals with advanced Friedreich ataxia and those with documented sleep apnea or nocturnal hypoventilation.

6.3 Restless legs and/or sleep related periodic limb movements

Sylvia Boesch, Sub Subramony, Mary G. Kearney and Louise Corben

6.3.1 Background

Restless legs and periodic limb movements during sleep are significantly more common in those with FRDA than in the general population: Restless legs syndrome (RLS) has been reported to affect 44.8% of adults with FRDA (14) compared to between 4% and 14% of the general population (15). Moreover, an international multi-center natural history study of people with FRDA found that sleep disturbance was reported by 59% (290/495) of adults and 45% (72/161) of children due to abnormal limb movements or leg cramps (14).

Types of abnormal limb movements

There are several types of abnormal limb movements:

a) Restless legs syndrome (RLS)
b) Periodic limb movements in sleep (PLMS)
c) Flexor spasms
d) Nocturnal leg cramps (NLCs)

RLS and PLMS are the most common types of abnormal limb movements in people with FRDA. It is important that the clinician makes an accurate diagnosis and does not confuse symptoms of RLS with flexor spasms or NLCs.

Restless legs syndrome

RLS is a sensory motor disorder, also known as Willis-Ekbom disorder (WED). It was first described in detail by Swedish neurologist Dr Karl Ekbom in the 1960s.

The symptoms of RLS are uncomfortable and unpleasant sensations in the legs, feet or arms associated with an urge to move them:

a) that are typified by relief of symptoms by moving the affected limb
b) occur during rest in the evening or at night
c) are associated with sleep disturbance or impairment
d) that cannot be explained by any other condition (e.g. arthritis, leg cramps, myalgias) (16).

RLS is a clinical diagnosis based on the above criteria. Given their multiple neurological and systemic issues, questions about symptoms of RLS may not be asked of people with FRDA such that RLS is currently underdiagnosed.

RLS is associated with sleep disturbance, a risk of anxiety or depression, and poorer overall health status. Polysomnography or actigraphy should be carried out in those with FRDA if there is suspicion of a sleep disorder.

Periodic limb movements in sleep

PLMS is repetitive, highly stereotyped limb movements that occur in non-rapid eye movement (non-REM) sleep. Typically, the periodic limb movements (PLMs) are characterized by extension of the big toe, often in combination with partial flexion of the ankle, the knee and sometimes the hip (16). PLMS is assessed using polysomnography, often done overnight in a sleep laboratory, or actigraphy, which uses an accelerometer in a wrist-worn device. Actigraphy has been validated to assess total sleep time and wakefulness after sleep onset (17). PLMs may also occur when the person is awake and they may be more intense.

If the number of PLMs is greater than 15 per hour in adults, or five per hour in a child over the entire night, it is considered pathological and may result in clinically disturbed sleep. PLMS may also cause daytime fatigue.

Note that periodic limb movement disorder (PLMD) is a separate condition and should not be diagnosed in conjunction with RLS. PLMS is seen in 80 to 90% of people with RLS but PLMS is not specific to RLS (18).

The relationship between PLMS and RLS is currently an active field of research (18).

Flexor spasms

A flexor spasm is a short, two to 10-second, very forceful involuntary muscle contraction, comprising dorsiflexion at the ankle and flexion at the knee and hip. It is a manifestation of upper motor neuron dysfunction. It may even be precipitated when vibration sensation is being tested, that is when a tuning fork is placed on the toes or when one is checking the Babinski sign. Flexor spasms usually occur when the person is awake, but may also wake a person from sleep. It can be precipitated by sensory stimuli such as bedclothes touching the feet or a full bladder.

Flexor spasms in people with specific disorders (other than FRDA) are typically associated with clinically evident spasticity and brisk reflexes. In FRDA they can occur in the absence of such signs because the peripheral neuropathy associated with FRDA will mask such upper motor neuron signs. Flexor spasms respond poorly to medication which makes them difficult to treat (See Chapter 3.4: Spasticity and Spasms)

Nocturnal leg cramps

NLCs cause a tight, knotted feeling in the legs that usually happens at night. NLCs are similar to spasms but usually last much longer, from several seconds to several minutes. If the cramp is severe, the affected muscle may be sore for days. NLCs are different from RLS and are present in 33% of the general population over 50 years of age.

6.3.2 Assessment

At their annual or biannual review, all individuals with FRDA should:

1) be asked about sleep disturbances and complete the Epworth sleepiness scale, a screening questionnaire for sleep disorders (https://epworthsleepinessscale.com/about-the-ess/)
2) be assessed for spasticity and spasms on physical examination.

6.3.3 Diagnosis and management

There is no evidence supporting specific management strategies for RLS or PLMS in individuals with FRDA. As such, the clinician should adopt general management guidelines for RLS and PLMS (19), with specific considerations for FRDA. In particular, it is critical that accurate diagnosis of RLS and PLMS guide management.

Diagnosis

- A diagnosis of RLS is based on patient history. However, the treating physician must be aware of the specific diagnostic criteria for RLS so they can ask the patient the correct questions. Sleep studies should be undertaken if there is any suspicion of a sleep disorder.
- A low serum ferritin, i.e. < 50 mcg/l may be associated with RLS (20). Therefore, serum ferritin in conjunction with iron studies, hematological and c-reactive protein blood tests should be part of the initial assessment.
- If PLMS is suspected, polysomnography or actigraphy should be done for confirmation of the diagnosis.
- Flexor spasms can be diagnosed from a history taken from the patient or family/carer and can be confirmed by clinical examination, as described above.
- NLC are diagnosed based on an accurate history, bearing in mind they do not usually occur every night.

Treatment of RLS

As RLS may be caused or precipitated by medication, an initial review of the person's current medication should be undertaken, specifically asking about selective serotonin reuptake inhibitors (SSRI), tricyclics, lithium and metoclopramide, as well as some hypnotic agents, before any treatment is recommended (21).

Regular physical activity, sleep hygiene, regular hours for going to bed, avoiding the use of electronic devices in bed and reducing or avoiding caffeine, smoking and alcohol should be recommended. A review of non-pharmacological treatments for RLS reported some evidence for clinically significant effects from exercise, acupuncture, pneumatic compression devices and near infrared light (21). Up to 65% of patients with RLS regularly use alternative approaches for symptom relief (21). We suggest that non-pharmacological therapy for RLS should be tried first, especially for milder cases, before proceeding to pharmacological therapy.

If iron levels are found to be low, iron supplements may be trialed (22). However, as mitochondrial iron overload can play a role in FRDA pathogenesis, patients who are given iron supplements should be followed up with frequent reassessment of their iron and ataxia status and discontinuation of iron if ferritin reaches acceptable levels.

If correctly diagnosed, RLS responds to pharmacological treatment. Gabapentin and pregabalin are currently the preferred pharmacological choice (19). L-dopa and the dopamine agonists pramipexole and ropinirole are only recommended for occasional use in RLS due to the high risk of augmentation, characterized by an increase in the severity of RLS. These drugs can cause RLS to come on earlier in the day and have a faster onset when at rest, cause symptoms to spread to the upper limbs and trunk, and are associated with a shorter duration of the effect of treatment. Therefore, the calcium channel blockers gabapentin and pregabalin are the preferred options.

Treatment of PLMS

PLMS may be a clinical symptom of RLS and should be treated if the individual has disabling symptoms. Dopaminergic drugs such as levodopa and dopamine agonists pramipexole and ropinirole are recommended. A positive response to these medications may help confirm the diagnosis.

Recommendations

Prevention/lifestyle

Should prevention/lifestyle versus none or medication be used for individuals with restless legs syndrome (RLS) symptoms with Friedreich ataxia?	**Strength**	**Level of evidence**
We conditionally recommend the use of prevention strategies/lifestyle changes (such as reduction of alcohol and nicotine use) over no prevention strategies/lifestyle changes or medication in individuals with Friedreich ataxia with RLS.	↑	⊕◯◯◯
Justification: RLS is a significant problem affecting 44.8% of adults with Friedreich ataxia. Lifestyle interventions such as a reduction of alcohol and nicotine especially in the evening may have an impact on RLS symptoms in general. Weighing up the balance between benefits, harms and costs, these measures appear to be acceptable. Regular physical activity, sleep hygiene, a regular time for going to bed, avoiding caffeine and the use of electronic devices in bed are likely to help RLS.		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia with symptoms of RLS. There is less known about prevention of RLS in children.		

Checking serum ferritin

Should serum ferritin levels be checked versus no checking be used for individuals reporting restless legs syndrome (RLS) with Friedreich ataxia?	**Strength**	**Level of evidence**
We conditionally recommend investigating serum ferritin levels in individuals with Friedreich ataxia presenting with symptoms of RLS over not checking ferritin. Serum ferritin is usually measured in combination with serum iron and transferrin saturation. Given that serum ferritin can be raised when	↑	⊕⊕◯◯

inflammation is present, acute and chronic inflammation should be assessed at the same time by doing a white cell count and measuring C-reactive protein (CRP).		
Justification: Research shows that serum ferritin levels are often low in those with RLS. Prior to testing serum ferritin levels, it is important to make sure that the individual with Friedreich ataxia fulfils the criteria for RLS. For a non-movement disorder neurologist, flexor spasms and RLS are easily confused. In fact, an individual may even report that they have RLS when in fact they have flexor spasm.		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia with symptoms of RLS. Restless legs are more common in those who have sleep disturbances. Females are generally more prone to have low ferritin levels than males.		

Complementary/alternative treatments

Should complementary/alternative treatments versus none or medication or lifestyle or physiotherapy be used for individuals with restless legs syndrome (RLS) symptoms with Friedreich ataxia?	**Strength**	**Level of evidence**
We suggest alternative/complementary treatments should *not* be used over no treatment/medication/lifestyle/physiotherapy for RLS in Friedreich ataxia.	↓	⊕◯◯◯
Justification: Based on no published evidence on complementary/alternative treatments in Friedreich ataxia, we suggest that regular physical activity, sleep hygiene, regular hours for going to bed, avoiding caffeine before bed and the use of electronic devices in bed may assist in managing RLS. A review of current medication is also suggested, which should focus in particular on selective serotonin reuptake inhibitors (SSRI), tricyclics and metoclopramide. RLS is a significant problem affecting 44.8% of adults with Friedreich ataxia. Complementary/alternative treatments may have undesirable side-effects for a person with Friedreich ataxia. There is no RCT on the use of complementary/ alternative treatments on RLS in Friedreich ataxia. However, if there are no undesirable side-effects, some people with RLS may find alternative treatments as helpful as medication and without the known side-effects of medication. It should be borne in mind when recommending any complementary/alternative treatments that they may be expensive and private insurers may not cover the cost for a person with Friedreich ataxia.		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia with symptoms of RLS. Restless legs are more common in those who have sleep disturbances.		

Iron supplementation

Should iron supplementation versus no supplementation be used for individuals with restless legs syndrome (RLS) and serum ferritin < 50 mcg/ml with Friedreich ataxia?	**Strength**	**Level of evidence**
We suggest iron supplementation could be trialed for treatment of RLS in individuals with Friedreich ataxia and serum ferritin < 50 mcg/ml, but only If other treatments have been tried and are not effective.	↑	⊕◯◯◯

Clinicians should only consider a trial of iron supplements if serum ferritin is < 50 mcg/ml and no acute or chronic inflammation is present, with close monitoring and a review to assess any adverse effects on ataxia after 3 to 6 months. If an individual has RLS and serum ferritin > 75 mcg/ml, they should not be given iron supplements.		
Justification: RLS is a significant problem affecting 44.8% of adults with Friedreich ataxia. Internationally, the recommendation for the treatment of RLS in the general population is to give iron supplements if ferritin is below 50-75 mcg/ml. However, in Friedreich ataxia, the pathophysiology of iron is not clear with iron overload in the mitochondria of cells and iron deficiency in the cytoplasm. Although there is currently no strong evidence, it is thought that iron supplementation may make ataxia worse. Therefore, we recommend that alternative treatments be given before iron is used to treat RLS. There have been no RCTs of iron supplementation to treat RLS in those with Friedreich ataxia. A survey on iron supplementation in RLS from expert clinicians involved in the care of those with Friedreich ataxia could not reach a consensus on this question. From the survey of 24 clinicians, 15 could not provide any information, one reported that iron did harm and six reported a small benefit. Therefore, the benefits of iron supplementation in the case of true iron deficiency with symptoms need to be considered against the side effects of iron supplementation. Due to the possibility of pathophysiological iron overload in the mitochondria in Friedreich ataxia, excess iron should be avoided. As RLS can interfere with the quality of sleep, it is an important symptom and effective treatment is desirable. However, the theoretical possibility of making ataxia worse in people with Friedreich ataxia is an important consideration.		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia with symptoms of RLS. Restless legs are more common in those who have sleep disturbances.		

Oral medication

Should oral medication versus none be used for individuals with idiopathic restless legs syndrome (RLS)/periodic limb movements in sleep (PLMS) with Friedreich ataxia?	**Strength**	**Level of evidence**
We conditionally recommend medication for individuals with Friedreich ataxia with RLS which interferes with sleep (with or without associated PLMS) over no medication. Gabapentin and pregabalin are the preferred choice of pharmacological treatment of RLS in Friedreich ataxia as they are as effective as levodopa but do not have the same side-effects. The dopamine agonists pramipexole and ropinirole may be helpful but should be used with caution in Friedreich ataxia due to the risk of augmentation of RLS symptoms. If PLMS is present it should be treated if the individual has disabling symptoms. Levodopa may be used intermittently when disabling RLS/PLMS symptoms are present since augmentation of RLS occurs only with long-term use. Given that levodopa alleviates	↑	⊕◯◯◯

symptoms of RLS rapidly, a 'test dose' of levodopa may be used to confirm a diagnosis of RLS in an individual with Friedreich ataxia.		
Justification: RLS is a significant problem affecting 44.8% of adults with Friedreich ataxia. However, there is uncertainty or variability in the opinion expressed about the value of medication to treat RLS. There are no RCTs addressing the impact of vitamins, baclofen, opioids or dopaminergic drugs, L-Dopa on sleep quantity/sleep benefit, impact on behavior, cognition, mood, degree of pain versus discomfort, or HRQOL in individuals with Friedreich ataxia with RLS. A survey of experts in Friedreich ataxia showed that the majority, 16 out of 24 clinicians, had no opinion or expertise in using these medications. Of those who had, 6 out of 8 clinicians, found that L-dopa had a modest effect on RLS. However, L-dopa can cause the undesirable side effect of augmentation which is where there is an increase in severity of RLS, faster onset of symptoms at rest, earlier onset of symptoms during the day, the symptoms spread to the upper limbs and trunk and shortened duration of treatment effect. Vitamin supplementation, baclofen and opioids and other dopaminergic drugs are of limited value in the treatment of restless legs in Friedreich ataxia.		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia with symptoms of RLS/PLMS. There is greater clinical experience with using medication for RLS in adults than children; therefore, even more caution needs to be exercised when prescribing medication for children.		

Lay summary

Lay summary of clinical recommendations for restless legs syndrome and/or periodic limb movements in sleep in Friedreich ataxia

Restless legs syndrome (RLS) and periodic limb movements in sleep (PLMS) are five times more common in those with Friedreich ataxia than in the general population.

Restless legs syndrome

The key symptoms of RLS are an overwhelming urge to move the legs, typically late in the day while resting, such as in bed before sleeping, that is often but not always associated with uncomfortable or unpleasant sensations in the legs. These symptoms can be relieved by moving the legs or walking. This can lead to disturbed sleep. The symptoms cannot be accounted for by other medical conditions such as leg swelling, muscle aches, arthritis or habitual foot tapping.

Periodic limb movements in sleep

PLMS are spontaneous, repeated, jerky movements, usually of the leg, which occur during sleep. They often interfere with sleep and cause fatigue and sleepiness during the day. The presence of PLMS is confirmed by doing a sleep recording called polysomnography. This is usually done in a sleep laboratory where the individual spends the night. More recently it has been done with an actigraphy, which uses an accelerometer in a device on the wrist. Both devices record muscle contraction in the lower leg while sleeping. PLMS are found in 4 out of 5 people with RLS.

Why these recommendations?

It is not known why individuals with Friedreich ataxia experience RLS and PLMS more than other people and there have not been specific guidelines to help people with Friedreich ataxia manage RLS or PLMS. Based on some research and our clinical experience, we recommend the following assessments and treatments for people with Friedreich ataxia and restless legs:

- The physician that cares for your Friedreich ataxia should explore symptoms of RLS during your visits.
- A healthy lifestyle, including reducing alcohol and smoking, regular physical activity, regular hours for going to bed, and avoiding caffeine and electronic devices before sleep may help with RLS.
- A full blood count (FBC) and serum ferritin in conjunction with iron studies and C reactive protein (CRP) should be taken since abnormal values of these chemicals may be seen in RLS and correcting them may relieve the symptoms of RLS.
- All your current medications to be checked, to see if the symptoms may be linked to a medication you are taking. Anti-depressants of the types known as selective serotonin reuptake inhibitors (SSRI) or tricyclics, lithium, the anti-sickness tablet metoclopramide and some sleeping tablets are known to cause RLS.
- Some medications may help RLS that interferes with sleep. Gabapentin and pregabalin are currently the preferred choice of medication. Oral iron should be used with caution and only started if serum ferritin is less than 50 mcg/ml. Dopaminergic drugs are not recommended for RLS – although they may help the symptoms at first, they may make the symptoms significantly worse in the long-term.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

It might be important for you to speak with your Friedreich ataxia healthcare professional if you are experiencing difficulties sleeping or have unexplained daytime fatigue or sleepiness. A healthy lifestyle with good sleep hygiene is recommended for those with Friedreich ataxia to try to avoid RLS and/or PLMs.

Who is this recommendation specifically for?

People with Friedreich ataxia who are experiencing restless legs before going to bed, sleep difficulties or unexplained fatigue.

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