Clinical Management Guidelines for Friedreich Ataxia

Chapter 3.11. Cognitive function in Friedreich ataxia

Contents

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3.11 Cognitive function in Friedreich ataxia

Gilles Naeije, Louise Corben and Jörg B. Schulz

This chapter describes the effects of Friedreich ataxia on cognitive function, the functional consequences of these effects, and recommendations for managing disturbance of cognitive function. In making recommendations, the authors were tasked with answering the question:

For individuals with Friedreich ataxia, what management strategies could be implemented for disturbance of cognitive function?

3.11.1 The effects of Friedreich ataxia on cognitive function

Cognition in Friedreich Ataxia (FRDA) is not as well studied as motor, sensory and gait disorders, and individuals with FRDA and their caregivers have low awareness of potential cognitive impairment (1). Past decades have unveiled a prominent role of the cerebellum and its efferent tracts, emerging from the cerebellum dentate nuclei (DN), in perception, higher cortical functions and affect modulation (2, 3). In regards to pathology, FRDA is hallmarked by progressive cerebellar DN atrophy (4). Thus, DN pathology in FRDA could have an impact on various domains of cognition through cerebello-cortical loops dysfunction.

Seminal investigations showed lower, but within normal limits, cognitive performance in individuals with FRDA compared to controls (5-7) and contemporary studies have reported normal mini-mental state examination (MMSE) scores (8-13) and slightly abnormal MOntreal Cognitive Assessment (MOCA) scores (14, 15). Yet, studies based on thorough neuropsychological evaluation found that individuals with FRDA displayed significant differences in almost all spheres of cognition, when specifically evaluated, compared to control participants.

Language fluencies are the most studied and individuals with FRDA show lower phonemic (12, 14-18) and semantic (7-9, 11, 15, 18, 19) fluencies, as well as lower action verbal fluencies (8, 9, 11) than controls. Attentional and executive function, measured by the Stroop Interference Test (8, 13, 20-23) or the trail making test (13, 15, 20, 23, 24) are also less efficient, and digit span assessment highlights poorer digit span forward (7, 11, 15, 16, 25-27) and backward (7, 11, 16, 25-27) recall. Similarly, memory assessments in individuals with FRDA show poorer performance in the California verbal learning test (11, 18, 27), the 10/36 spatial recall test (11, 18, 27) and in logical memory evaluations (11, 18) compared to controls. Visuospatial abilities, assessed in fewer studies, are also altered (6, 11, 12, 18, 19, 28).

Emotion recognition and social cognitive abilities are poorly characterized, but individuals with FRDA display less skill in facial expression, emotion recognition (11, 15, 18, 21) and in identifying social faux-pas (27). Thus, individuals with FRDA do not perform as well as controls in most cognition domains: language, attentional and executive functions, memory, visuospatial, emotion recognition and social cognitive abilities (1). This widespread involvement suggests that the cerebellum is the common factor. The combination of relatively mild but global higher neocortical dysfunction is characteristic of the cerebellum cognitive affective syndrome, a *thought dysmetria* that hampers language, emotions, memory, attention, visuospatial and executive functions (29, 30).

3.11.2 Functional consequences of disturbance of cognitive function

In addressing the sensitive issue of cognitive function in people with FRDA it should be noted that the deficits described do not generally preclude a person with FRDA from participating in education at school and college/university, gaining meaningful and even cognitively demanding employment, partnering and raising a family (31). Cognitive disorders in FRDA are considered to be relatively subtle and do not cause obvious functional impairment, which explains why it is often overlooked (32). However, even if missed by classic screening tools, cognitive and affective impairments may affect the ability of individuals with FRDA to study, work and develop their full potential, both intellectually and socially. Thus, cognitive impairments should be considered when difficulties arise in any of those areas.

There is limited evidence on the potential progression of cognitive impairments in individuals with FRDA and dedicated studies are needed (1). Yet, there seems to be a correlation between structural alterations of the dentate nuclei, dentato-rubral tracts and posterior cerebellar lobes and cognitive performance (33, 34). Language fluency as well as attention and processing speed worsen over time (7, 8), and there is a relationship between the magnitude of cognitive impairment and ataxia severity (35). This suggests that cognitive impairment relates to cerebellar pathology in FRDA and that cognitive disorders may appear as the disease progresses, with a severity that is correlated with the extent of cerebellar ataxic symptoms.

3.11.3 Management of disturbance of cognitive function

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	↓↓		

Education

Should education regarding possible cognitive impairment versus no education regarding possible cognitive impairment be used for all individuals with Friedreich ataxia?	**Strength**	**Level of evidence**
We suggest development and implementation of an educational program for affected individuals and their families and carers to improve information about the potential for, and management of, cognitive dysfunction in individuals with Friedreich ataxia.	↑	⊕◯◯◯
Justification: There is increasing evidence of cognitive dysfunction in individuals with Friedreich ataxia that has the potential to affect academic, vocational and interpersonal pursuits. There is a need to identify and address this potential, particularly as individuals with Friedreich ataxia may be unaware of the possibility of cognitive dysfunction.		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia and their parents, carers, partners and family.		

Neuromodulation

Should active neuromodulation (tDCS, TMS) versus sham neuromodulation be used for all individuals with Friedreich ataxia?	**Strength**	**Level of evidence**
We recommend that clinicians should *not* use active neuromodulation (tDCS, TMS) as part of clinical practice to improve cognitive function in individuals with Friedreich ataxia.	↓↓	⊕◯◯◯
Justification: There are no data available to support positive effects of active neuromodulation to improve cognitive function in individuals with Friedreich ataxia.		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia with concerns about cognitive function.		

Lay summary

Lay summary of clinical recommendations for disturbance of cognitive function in Friedreich ataxia

Cognition is a term that relates to thinking processes such as remembering, judging, decision making and problem solving. These processes are involved in how we comprehend, understand and interact with the world around us. There is increasing evidence that cognition may be affected in Friedreich ataxia, with possible important consequences. However, individuals with Friedreich ataxia and their carers may not be aware that cognitive problems can arise with Friedreich ataxia.

Why these recommendations?

We suggest that educational programs for individuals with Friedreich ataxia and their families may help to improve understanding of the potential cognitive problems related to Friedreich ataxia and what can be done to address these problems. However, there is currently no research evidence to support this recommendation. There is a need, therefore, to do research to find out if educational programs on cognition would help individuals with Friedreich ataxia or their carers to identify, understand and manage any cognitive difficulties that may happen.

Education programs might be helpful to individuals with cognitive difficulties that affect their ability to study, work or have successful personal relationships.

In addition, there is some evidence in similar conditions to Friedreich ataxia that stimulation to the brain may be of benefit in improving cognition. However, this has not been shown in people with Friedreich ataxia, so we do not recommend brain stimulation at present.

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 healthcare professional about Friedreich ataxia and potential associated cognitive problems. This is particularly important if you, or the person you care for, are having problems managing work, study or personal relationships which may be related to changes in cognition.

Who are these recommendations specifically for?

These recommendations are for all individuals with Friedreich ataxia and their carers, partners and family.

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