

QUESTION

Should monitoring at least once per year vs. informal monitoring be used for ambulant individuals with Friedreich ataxia?

POPULATION:	ambulant individuals with Friedreich ataxia
INTERVENTION:	monitoring at least once per year
COMPARISON:	informal monitoring
MAIN OUTCOMES:	Independence of ambulation; Balance; Falls; Walking capacity; Quality of life ;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Gait instability is the most frequently reported initial symptom in individuals with FRDA, occurring as the first symptom in 76 - 88% of individuals (Reetz et al, 2015). Mobility typically declines, with loss of mobility for individuals with onset <15 years of age typically 11.5 years after first symptom onset; 18.3 years for individuals with onset 15-24 years of age and 23.5 years for individuals with onset >24 years (Rummeley et al, 2020).</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of the topic.</p> <p>1/7 indicated the consequences of the disturbance of strength, balance, mobility and reduction of falls were probably serious, 5/7 indicated serious, 1/7 indicated didn't know if serious.</p> <p>1/7 indicated the consequences of the disturbance of strength, balance, mobility and reduction of falls were probably not urgent, 1/7 indicated probably urgent, 5/7 indicated urgent.</p> <p>1/7 indicated the consequences of the disturbance of strength, balance, mobility and reduction of falls were probably a priority, 6/7 indicated priority. (Aug 2020).</p> <p>In a public forum entitled "Voice of the patient", held on 2 June 2017 in the USA to inform the United States Food and Drug Administration approximately 400 attendees (in-person and online) were asked to choose top three symptoms that would be most meaningful to treat. 55% of people chose improving balance or improved walking as two of their top symptoms (weblink: http://curefa.org/pdf/news/FA-Voice-of-the-Patient.pdf).</p>

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Trivial 	<p>A search of 4 databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified randomized, non-randomized</p>	<p>As seen in their clinical practice, there are many factors that may</p>

<ul style="list-style-type: none"> ○ Small ● Moderate ○ Large ○ Varies ○ Don't know 	<p>controlled, cohort and case studies published from 2014 through to 24 September 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	<p>influence loss of ambulation in individuals with FRDA, including spasticity, balance, ataxia, strength, joint range of movement, strength and cardiovascular fitness or endurance. Non-physical factors may also influence mobility decline. These can include but are not limited to fear of falling, engagement in exercise and social support structures.</p> <p>The Ataxia UK Medical Guidelines also recommends regular follow-up by a physiotherapist to preserve mobility and provide advice on walking aids at the different stages of the condition for all progressive ataxias including individuals with FRDA. 'Regular' physiotherapist follow-up is not defined in the Ataxia UK Medical Guidelines; however, the guidelines recommend 6-12 monthly reviews from a neurologist or specialist ataxia neurologist to monitor progression of the conditions and identify any new symptoms requiring treatment (de Silva et al, 2019).</p>
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Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know 	<p>A search of 4 databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified randomized, non-randomized controlled, cohort and case studies published from 2014 through to 24 September 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	<p>There are no risks associated with regular monitoring (at least once per year) for individuals with FRDA.</p>

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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<ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate ○ High ○ No included studies 	<p>No published evidence.</p>	<p>Although there is no published evidence directly supporting regular monitoring of ambulation, annual decline in ambulation is apparent (Mine et al, 2018; Zesiewicz et al, 2017).</p>
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Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																		
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability 	<table border="1" data-bbox="518 659 1419 1101"> <thead> <tr> <th>Outcomes</th> <th>Importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Independence of ambulation - not measured</td> <td>IMPORTANT^a</td> <td>-</td> </tr> <tr> <td>Balance - not measured</td> <td>IMPORTANT^b</td> <td>-</td> </tr> <tr> <td>Falls - not measured</td> <td>CRITICAL^c</td> <td>-</td> </tr> <tr> <td>Walking capacity - not measured</td> <td>IMPORTANT^d</td> <td>-</td> </tr> <tr> <td>Quality of life - not measured</td> <td>CRITICAL^e</td> <td>-</td> </tr> </tbody> </table> <p data-bbox="562 1138 1388 1398"> a. Identified as critical (1/6), important (3/6) and low importance (2/6) by people with FA and critical by expert authors on this topic. b. Identified as critical (2/5) and important (3/5) by people with FA and important by expert authors on this topic. c. Identified as critical (3/5) and important (2/5) by people with FA and important by expert authors on this topic. d. Identified as critical (2/6), important (3/6) and low importance (1/6) by people with FA and important by expert authors on this topic. e. Identified as critical (3/6) and important (3/6) by people with FA and critical by expert authors on this topic. </p>	Outcomes	Importance	Certainty of the evidence (GRADE)	Independence of ambulation - not measured	IMPORTANT ^a	-	Balance - not measured	IMPORTANT ^b	-	Falls - not measured	CRITICAL ^c	-	Walking capacity - not measured	IMPORTANT ^d	-	Quality of life - not measured	CRITICAL ^e	-	
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Walking capacity - not measured	IMPORTANT ^d	-																		
Quality of life - not measured	CRITICAL ^e	-																		

Balance of effects		
Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know 	<p>No published evidence directly addressing the PICO question.</p> <p>Although there is no published evidence directly addressing the effectiveness of monitoring mobility for ambulant individuals with FRDA, annual decline in comfortable gait speed of 8% and in fast speed of 13.9% was seen in eight individuals with FRDA with a disease duration ranging between 13-36 years (Zesiewicz et al, 2017).</p>	<p>A survey designed to systematically collect expert-based opinions from clinicians involved in developing the recommendations for this topic and providing clinical care for individuals with Friedreich ataxia, was conducted. Clinical experts from Australia, Europe, UK, South America, Canada and the USA were asked to consider the harms/benefits of annual assessment/screening as a management strategy for ambulant individuals.</p> <p>Reflecting on the impact of annual assessment/screening on <u>Independence of ambulation</u>, 100% (2/2) clinical experts reported a benefit (large, moderate or small).</p> <p>Reflecting on the impact on <u>Balance</u>, 100% (2/2) clinical experts reported a benefit. Reflecting on the impact on <u>Falls</u>, 100% (2/2) clinical experts reported a benefit.</p> <p>Reflecting on the impact on <u>Walking capacity</u>, 100% (2/2) clinical experts reported a benefit. Reflecting on the impact on <u>Quality of life</u>, 100% (2/2) clinical experts reported a benefit.</p>

Acceptability		
Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know 	<p>No published evidence.</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if the intervention was acceptable (weighing up the balance between benefits, harms and costs).</p> <p>4/4 indicated that monitoring at least once per year was reasonable. (Aug 2020).</p>

SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ●
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CONCLUSIONS

Recommendation

For individuals with Friedreich ataxia who are ambulant (with or without an aid), we recommend regular monitoring of ambulation and contributing physical and non-physical factors for mobility decline (such as balance, strength, lower limb spasticity and fear of falling) at least once per year over less regular or informal monitoring.

Justification

Although there is no published evidence directly addressing the effectiveness of monitoring mobility for ambulant individuals with FRDA, annual decline reported in published papers and seen in clinical practice warrants regular (at least annual) monitoring and assessment of mobility. This recommendation is consistent with recommendations made in the Ataxia UK Medical Guidelines (de Silva et al, 2019).

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia who are ambulant.

Research priorities

Although there is no published evidence directly examining regular monitoring of ambulation in individuals with FRDA, this is clearly best practice. Further research should focus on management strategies and treatments for ambulatory decline, to prevent loss or delay the loss of ambulation.

References

de Silva RN, Greenfield J, Cook A, Bonney H, Vallortigara J, Hunt B, et al. Guidelines on the diagnosis and management of progressive ataxia in adults. *Orphanet J Rare Dis.* 2019;14:51.

Milne S, Kim S, Murphy A, et al. Longitudinal change of gait and balance in individuals with Friedreich ataxia. *Neurology* 2018;90:Abstract S18.008.

Reetz K, Dogan I, Costa AS, Dafotakis M, Fedosov K, Giunti P, et al. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. *Lancet Neurol.* 2015;14(2):174-82.

Rummev C, Farmer JM, Lynch DR. Predictors of loss of ambulation in Friedreich's ataxia. *EClinicalMedicine.* 2020;18:100213.

Zesiewicz TA, Stephenson JB, Kim SH, Sullivan KL, Jahan I, Huang Y, et al. Longitudinal gait and balance decline in Friedreich's Ataxia: A pilot study. *Gait Posture.* 2017;55:25-30.