QUESTION

Should serum ferritin levels be checked vs. no checking be used for patients with RLS symptoms with Friedreich ataxia?	
POPULATION:	patients with RLS symptoms with Friedreich ataxia
INTERVENTION:	serum ferritin levels be checked
COMPARISON:	no checking
MAIN OUTCOMES:	Impact on sleep quality/ arousal ; Impact on sleep quantity/ sleep benefit; Impact on behaviour, cognition, mood; Degree of pain vs discomfort;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Data from the FA Clinical Outcome Measures (FA-COMS) registry (Lynch, 2017) found: 44.8% (312/696) of adults and 34.9% (110/315) of children reported restless legs; 75.0% (522/696) of adults and 55.6% (175/315) of children reported leg spasms. By comparison, restless legs affect between 4% and 14% of the general population (Ohayon et al, 2012). For individuals who reported sleep disturbance: Restless legs were present in 46.3% (229/495) of adults and 32.9% (53/161) of children, and leg cramps in 58.6% (290/495) adults and 44.7% (72/161) of children (Lynch, 2017). Serum ferritin and RLS: Individuals with FRDA with lower serum ferritin levels have a higher prevalence of RLS symptoms (Frauscher et al, 2011).	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of restless legs. 2/7 indicated that the problem was serious, 4/7 indicated probably serious, 1/7 indicated probably not serious. 2/7 indicated that the problem was urgent, 4/7 indicated probably urgent, 1/7 indicated probably not urgent. 3/7 indicated that the problem was a priority, 3/7 indicated probably a priority, 1/7 indicated probably not a priority. (Aug 2020)

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 30 October. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 30 October. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	No published evidence.	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		

Outcomes	Importance	Certainty of the evidence (GRADE)
Impact on sleep quality/ arousal - not measured	IMPORTANT[a]	-
Impact on sleep quantity/ sleep benefit - not measured	IMPORTANT[a]	-

Impact on behaviour, cognition, mood - not measured	IMPORTANT[a]	-
Degree of pain vs discomfort - not measured	CRITICAL[b]	-

a. Identified as critical (1/6), important (4/6) and low importance (1/6) by people with FA and important by expert authors on this topic
b. Identified as critical (3/6), important (2/6) and low importance (1/6) by people with FA and important by expert authors on this topic

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ 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	No published evidence.	A survey designed to systematically collect expert-based opinions from clinicians involved in the development of these guidelines 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 assessing ferritin levels for people with Restless Leg Syndrome. Reflecting on the impact of on Impact on **sleep quality/arousal**, 29.17% (7/24) clinical experts reported a benefit (large, moderate or small), 4.17% (1/24) reported no effect and, 4.17% (1/24) reported observing a harm (large, moderate or small). 15 clinicians could not provide any information on this outcome. Reflecting on the impact on **sleep quantity/sleep benefit**, 29.17% (7/24) clinical experts reported a benefit, 4.17% (1/24) reported no effect and, 4.17% (1/24) reported observing a harm. 15 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **behaviour, cognition, mood**, 20.83% (5/24) clinical experts reported a benefit, 12.5% (3/24) reported no effect and, 4.17% (1/24) reported observing a harm. 15 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **Degree of pain versus discomfort**, 16.66% (4/24) clinical experts reported a benefit, 16.67% (4/24) reported no effect and, 4.17% (1/24) reported observing a harm. 15 expert clinicians could not provide any information on this

		outcome.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No published evidence.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if checking serum ferritin levels in people with restless legs syndrome was acceptable (weighing up the balance between benefits, harms and costs). 2/3 indicated the intervention was acceptable, 1/3 indicated more information on the benefits and potential harms was required. (Aug 2020).

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	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
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
○	○	○	●	○

CONCLUSIONS

Recommendation

We conditionally recommend investigating serum ferritin levels in individuals with FRDA 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 FRDA 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.

Implementation considerations

Not relevant

Research priorities

Further studies in larger cohorts should be undertaken to justify a recommendation to test serum ferritin levels in those with RLS, keeping in mind the need to exclude acute and chronic inflammation.

References

Lynch D. FA Clinical Outcome Measures (FA-COMS) Registry (unpublished data): clinicaltrials.gov; 2017 [Available from: https://clinicaltrials.gov/ct2/show/NCT03090789

Frauscher B, Hering S, Hogl B, Gschliesser V, Ulmer H, Poewe W, et al. Restless legs syndrome in Friedreich ataxia: a polysomnographic study. Mov Disord. 2011;26(2):302-6.

Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Med Rev. 2012;16(4):283-95.