Treatment for speech disorder in Friedreich ataxia and other hereditary ataxia syndromes (Protocol)

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**Treatment for speech disorder in Friedreich ataxia and other hereditary ataxia syndromes**

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**ABSTRACT**

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of interventions for speech impairment in people with Friedreich ataxia and other hereditary ataxias.

**BACKGROUND**

Friedreich ataxia, an autosomal recessive neurodegenerative disorder, is the most common hereditary ataxia, affecting approximately 1:40000 people (Delatycki 2000). There are also several other known autosomal dominant (for example spinocerebellar ataxias (SCAs)) and recessive hereditary ataxias that can affect speech. In the case of many hereditary ataxias, speech difficulties have been documented as a common outcome of disease progression, typically manifesting in dysarthria (slurred speech). In the case of Friedreich ataxia (Folker 2010) and SCA (Schalling 2007) individuals often present with a reduced rate of speech, vocal instability and imprecise consonants. Dysarthria affects the ability to communicate, to participate in society and reduces quality of life. Given the significant deleterious impact of speech disorder on an individual’s functioning, a strong body of evidence is required for the treatment of speech impairment in these conditions.

Description of the condition

The major clinical features of Friedreich ataxia include progressive ataxia (100%), dysarthria (95%), scoliosis (78%), cardiomyopathy (65%), diabetes mellitus (8%) and foot deformity (74%) (Delatycki 1999). Onset is generally in childhood at an average age of 10 years, with the individual becoming non-ambulant at an average age of 19 years, and life expectancy being markedly reduced. The many recognised SCAs vary in their clinical presentation and age of onset, and some are known to influence speech function (Schalling 2007). The prevalence of speech disorder in SCA is not yet known. There are also a number of rare autosomal recessive hereditary ataxias where little is known on the clinical features relating to speech. Speech impairment in Friedreich ataxia and SCA varies depending on a number of factors (for example severity of other clinical features, stage of disease progression) and is often characterised by reduced or uncontrolled variation in pitch, a slower rate of speech and imprecise production of sounds (slurred speech) and reduced intelligibility. Deleterious consequences can also go beyond the physiological impairment level and lead to activity limitation (for example communicating over the telephone).
and can be influenced by key environmental factors (for example communicating in noisy environment) (Hartelius 2007). Limited data exist on the speech profiles of other recessive hereditary ataxias.

**Description of the intervention**

This review will focus on the effects of speech therapy in people with hereditary ataxias, including Friedreich ataxia. Speech therapy may take the form of instrumental intervention, traditional drill based therapy techniques or a combination of both.

**How the intervention might work**

The effectiveness of an intervention can best be conceptualised using the International Classification of Functioning, Disability and Health (ICF-DH) (WHO 2001). At an impairment level, speech therapy can improve the capacity of individuals with a hereditary ataxia to communicate orally. This can be achieved by enhancing the production of sounds and words, by improving breath support for speech, and by restoring an individual’s speech to premorbid levels and maintaining adequate levels of intelligibility. At an activity and participation level, intervention could aid an individual’s capacity to participate in social and professional settings that require effective communication skills. Finally, at an environmental level, modification of an individual’s communication environment (for example educating communication partners on effective communication skills) could lead to improved communication outcomes. Improvement in these three domains would enable people with hereditary ataxias to actively participate in society and maintain personal and professional relationships.

**Why it is important to do this review**

Dysarthria (speech disorder) is a primary feature of Friedreich ataxia, with estimates of prevalence ranging from 91% (Dürr 1996) to 100% (Schols 1997; Folker 2010). An earlier study by Harding 1981 showed dysarthria to be present in all participants 10 years after onset, suggesting that speech disorder is an inevitable outcome of disease progression. Speech disorder is also a key component of other hereditary ataxias including SCA (Schalling 2007) however prevalence rates are not yet known. The likely presence of speech impairment in all individuals with a hereditary ataxia necessitates the development of effective and proven therapies for ameliorating this aspect of the disorders.

**OBJECTIVES**

To assess the effects of interventions for speech impairment in people with Friedreich ataxia and other hereditary ataxias.
Primary outcomes

Our primary outcome measure will be the percentage change in improvement of overall speech production at one week or greater post intervention as measured by any validated speech assessment tool.

Secondary outcomes

1. Change in isolated movement, objective and subjective measures of speech production (for example acoustic analysis of nasality; articulation; laryngeal function; respiratory function, oral motor function). Measured at least one week after treatment.
2. Change in quality of life scores related to communication as measured by validated communication assessments such as the Voice Handicap Index (Ordinal variables). Measured at least one week after treatment.
Secondary outcomes (3 to 6) were considered to capture longer term effects of therapy and thus were included if they were administered at a minimum of one month or more post therapy completion.
3. Generic quality of life measures (for example Short Form-36 (SF36)).
4. Adverse effects.
5. Burdens (for example demands on caregivers, frequency of tests, restrictions on lifestyle).
6. Economic outcomes (for example cost and resource use).

Search methods for identification of studies

We will search the Cochrane Neuromuscular Disease Group Specialised Register using the following terms: Friedreich ataxia, spinocerebellar ataxia, dentatorubral-pallidoluysian atrophy, Myoclonic Epilepsies, Progressive, autosomal dominant spastic ataxia, episodic ataxia, ataxia and Charlevoix-Saguenay, Spinocerebellar Degenerations, Marinesco-Sjogren, Ataxia and oculomotor apraxia type 2, Ataxia and oculomotor apraxia type 1, Ataxia and vitamin E deficiency, Ataxia-telangiectasia, Joubert syndrome and speech, articulate or voice or vocal or communication, Speech, Voice Disorders, Voice, Vocal Cord Paralysis, Vocal Cords, dysarthria, dysphonia, anarthria, dysprosody, Speech Disorders.
We will also search The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue, current issue), MEDLINE (1966 to present), EMBASE (1980 to present), CINAHL (1937 to present), PsycINFO (1806 to present), Education Resources Information Center (ERIC) (1965 to present), Linguistics and Language Behaviour Abstracts (LLBA) (1973 to present) and Dissertation Abstracts (1980 to present). Conference abstracts will be scanned for relevant studies. All references in the identified trials will be checked and authors contacted to identify any additional published or unpublished data.

Electronic searches

The following databases will be searched from inception: Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library
MEDLINE
CINAHL
Dissertation Abstracts
EMBASE
ERIC
Linguistics and Language Behaviour Abstracts (LLBA)
PsycINFO
The search strategy for MEDLINE can be found in Appendix 1.

Searching other resources

We will request information on unpublished trials from authors of published studies, and experts and information groups in the areas of linguistics and speech therapy.

Data collection and analysis

A summary of findings table will be included, incorporating the key primary and secondary outcome measures. The table will also include data on trial (for example design, duration of follow-up) and participant characteristics.

Selection of studies

Two authors (AV and JF) will independently screen titles and abstracts to exclude reports that are obviously irrelevant. In cases of uncertainty the full text article will be evaluated. Two review authors (AV and JF) will evaluate the full text article of potentially eligible studies. In the event of disagreement over inclusion of a particular paper, a consensus will be formed by AV, JF and BM re-assessing the inclusion criteria together.

Data extraction and management

Two authors (AV and JF) will perform data extraction and will independently enter data onto a data extraction form. Discrepancies will be resolved by the third author (BM). Two authors will check data, one will enter them into Review Manager (RevMan) and the other check data entry.

The data extraction form will include the following items:
1. General information: published/unpublished, title, authors, reference/source, contact address, country, language of publication, year of publication.
2. Trial characteristics: design, duration of follow-up, method of randomization, allocation concealment, blinding (participants, people administering treatment, and outcome assessor).
3. Participants: age, sex and any other recorded baseline characteristics, inclusion and exclusion criteria, total number, number in
each group, disease severity, withdrawals and losses to follow-up (reasons and description).

4. Intervention(s) and outcome(s): placebo included, type of speech therapy, duration, frequency, interval, comparison intervention(s), co-treatment(s), the number and type of adverse events, other outcomes reported in the trial.

We will resolve differences in data extraction by consensus, and by referring back to the original article. When necessary, we will request further information from the authors of the primary studies.

**Assessment of risk of bias in included studies**

AV and JF will independently assess all included studies for risk of bias. We will grade the items according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) and present judgements for each included trial in a 'Risk of bias' table. We will assess trials for sequence generation, allocation concealment, blinding (participants and outcome assessors), incomplete outcome data, intention-to-treat analysis, participant losses, selective outcome reporting and other sources of bias. We will then make a judgement on each of these criteria relating to the risk of bias where 'Yes' indicates a low risk of bias, 'No' a high risk of bias and 'Unclear' an unknown risk of bias or that the entry is not relevant to a study.

**Measures of treatment effect**

Measures of treatment effect for primary outcome measures will rely on the outcome measures provided by the study authors including; improvements in isolated sound, single word, sentence or conversation level productions. We will rate these outcomes using instrumental and perceptual outcome measures. We will analyse data using the Cochrane statistical package Review Manager 5 (RevMan 2008). For dichotomous data we will derive risk ratios (RR) and 95% confidence intervals (CIs) for each outcome. For continuous variables we will calculate mean differences and 95% CIs for each outcome. We will use a fixed-effect model to calculate pooled estimates and their 95% CIs, however, if the model yields large standard errors (i.e., the studies are not homogenous), a random-effects model will be considered.

**Unit of analysis issues**

Each participant may produce data from one or more of the measures of effect. For crossover designs, there is a potential source of bias if the training arm precedes no training because of the effect of conditioning. For this reason, if a difference in treatment effects and its standard error is available from a crossover trial it will be combined with the results of parallel group studies using the GIV facility in RevMan. If these data are not available, only the first arm of the study will be analysed.

**Dealing with missing data**

In the event of missing data within published studies, authors AV and JF will contact primary investigators for assistance and information.

**Assessment of heterogeneity**

We will assess consistency of results using the I² statistic for heterogeneity (Higgins 2009). I² is a quantity describing approximately the proportion of variation in point estimates that is due to heterogeneity of a sample rather than error in sampling of the population. For values greater than 50%, we will examine forest plots for differences between trials which could explain heterogeneity. A test of homogeneity will be used to determine that the heterogeneity is genuine. In the event of too few studies being available to make this test feasible, a random-effects model will be applied.

**Assessment of reporting biases**

Publication bias and other reporting biases will be investigated using funnel plots if there is a sufficient number of studies. Funnel plot asymmetry will be evaluated visually and using formal tests for funnel plot asymmetry. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random-effects model, we will perform further meta-analyses using a fixed-effect model.

**Data synthesis**

We will perform meta-analysis only where studies employ similar interventions and where study populations are clinically homogenous.

To enable the combination of studies measuring the same outcome using different methods, we will summarise continuous data using mean differences. Binary outcomes are likely to be common in early reports within the field (e.g. improved outcome versus no change/worse). We will analyse data by calculation of the risk ratio with a 95% confidence interval.

**Subgroup analysis and investigation of heterogeneity**

In reference to patient characteristics, where possible, we will undertake subgroup analysis by modus of inheritance and causative gene or chromosomal locus, type of ataxia, and the severity of dysarthria. Heterogeneity will also be considered in reference to study design and implementation characteristics, including but not limited to methods of recruitment and randomization, and methods of implementing therapy.
Sensitivity analysis

We will use sensitivity analysis to assess the robustness of the overall findings by examining the impact of study quality, for example lack of allocation concealment or high rates of loss to follow-up, the impact of missing data or the impact of imputations, and the rigor of eligibility criteria employed in the study. We will also evaluate the possibility of one or more large studies dominating the results.

ACKNOWLEDGEMENTS

We wish to thank the members of the Cochrane Neuromuscular Disease Review Group for their assistance and acknowledge the patients of the Friedreich Ataxia Clinic, Monash Medical Centre, Melbourne, Australia.

REFERENCES

Additional references

Delatycki 1999

Delatycki 2000

Dierr 1996

Folker 2010

Harding 1981

Hartelius 2007

Higgins 2008

RevMan 2008

Schalling 2007

Schols 1997

WHO 2001

* Indicates the major publication for the study
Appendix 1. Search Terms

The search strategy below will be used for MEDLINE:
1. Friedreich's ataxia.mp. or Friedreich Ataxia/
2. spinocerebellar ataxia.mp. or Spinocerebellar Ataxias/
3. dentatorubral-pallidoluysian atrophy.mp. or Myoclonic Epilepsies, Progressive/
4. autosomal dominant spastic ataxia.mp.
5. episodic ataxia.mp.
7. Marinesco-Sjögren.mp. or Spinocerebellar Degenerations/
8. Ataxia and oculomotor apraxia type 2.mp.
9. Ataxia and oculomotor apraxia type 1.mp.
10. Ataxia and vitamin E deficiency.mp.
11. Ataxia-telangiectasia.mp. or Ataxia Telangiectasia/
13. or/1-12
14. ((speech or articulat$ or voice or vocal or communicat$)
15. speech/
16. Voice Disorders/ or Voice/
17. Vocal Cord Paralysis/ or Vocal Cords/
18. (dysarth$ or dysphon$ or anarth$ or dyspros$).mp.
19. Dysarthria/
20. Dysphonia/
21. Speech Disorders/
22. or/14-21
23. randomized controlled trial.pt.
24. controlled clinical trial.pt.
25. randomized.ab.
26. placebo.ab.
27. drug therapy.fs.
28. randomly.ab.
29. trial.ab
30. groups.ab.
31. or/23-30
32. (animals not (animals and humans)).sh.
33. 31 not 32
34. 13 and 22 and 33

Terms and filters will be modified as appropriate for other databases.
HISTORY
Protocol first published: Issue 1, 2011

CONTRIBUTIONS OF AUTHORS
Adam Vogel had the original idea for the review and wrote a draft of the protocol. Joanne Folker and Bruce Murdoch edited the text. The authors developed the search strategy in concert with the Cochrane Neuromuscular Disease Review Group.

DECLARATIONS OF INTEREST
None of the three authors has a conflict of interest.

SOURCES OF SUPPORT

Internal sources
• none, Not specified.

External sources
• none, Not specified.