

# Cognitive impairment in Friedreich's ataxia

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## SUMMARY STATEMENT

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## REQUEST

Are there cognitive deficits associated with Friedreich's ataxia?

## REQUESTED BY

**Louise Corben**, Occupational Therapy, Monash Medical Centre, Clayton.

## METHODOLOGY

### Search Strategy

The Centre for Clinical Effectiveness defines the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined National Health and Medical Research Council (NHMRC, 2000) criteria (see Appendix 1).

First, we search for systematic reviews, evidence based clinical practice guidelines, health technology assessments and randomised controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable or have other methodological difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements in our reports, we do not critically appraise them. Such studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

### Details of Evidence Request

Exposure: Friedreich's ataxia  
Comparison: persons without Friedreich's ataxia  
Outcomes: cognitive impairments

### Search terms

(see Appendix 2 for exact search strategy)

Exposure terms: Friedreich's ataxia  
Comparison terms: (none)  
Outcome terms: Cognition disorders, cognitive impairments, cognitive deficits

## **Resources Searched**

We searched the following databases:

The Cochrane Library (CD-ROM) - 2001 Issue 1

MEDLINE (OVID)- 1966 to February Week 1 2001

PREMEDLINE (OVID) – April 2, 2001

CINAHL (OVID) - 1982 to March 2001

Current Contents (OVID) - 1993 Week 26 to 2001 Week 16

SocioFile – 1974 to February 2001

PsycINFO – 1967 to March week 3 2001

## **Refinements, Searching & Reporting Constraints**

We included articles that were available to us on April 12, 2001.

## RESULTS

From our sources we identified five potentially relevant articles. After examination of the articles, three were excluded for the following reasons:

Reason for exclusion	Number
Case reports (level IV evidence)	1
Non-English articles	2
<b>Total</b>	<b>3</b>

Two articles then remained for appraisal. These studies are classified as follows:

Study Design	Number included
Systematic reviews or meta-analyses	0
Evidence-based clinical practice guidelines	0
Randomised controlled trials	0
Pseudorandomised controlled trials	0
<b>Controlled trials, cohort or case-control analytic studies</b>	<b>2</b>
<b>Total</b>	<b>2</b>

Based on our refinements, searching and reporting constraints, we are reasonably confident these articles represent the most relevant findings published to date.

The examination of an association between a disease/exposure (in this case, Friedreich's ataxia) and an adverse outcome (cognitive impairment) is referred to as 'aetiology'. Typically, two study designs are practical in an aetiology study: a cohort study or a case control study. A cohort study prospectively follows groups (cohorts) of patients who are and who are not exposed to the treatment/exposure/disease until the development of the outcome of interest. Case-control studies retrospectively identify the disease state of interest in patients described as 'cases', and those without the disease ('controls') are selected for a comparison. Note that a randomised controlled trial is usually not possible in an aetiology study (in this case, it would not be possible to randomise patients to Friedreich's ataxia or not), thus cohort and case-control study designs are the highest available evidence for this type of question. However it is more difficult to control for bias in these study types because patient characteristics that may increase the risk of having the outcome (confounders) may not be evenly distributed between groups in a cohort or case-control study but would be expected to be evenly distributed between groups if randomisation was adequate in a randomised controlled trial.

The two articles included for critical appraisal describe case-control studies where cognitive measurements from patients with Friedreich's ataxia were compared with measurements from normal controls.

## EVIDENCE SUMMARIES

### Format

Evidence summaries are presented as spreadsheets attached to this report. Each spreadsheet contains the article citation, details of the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

## REFERENCES

### ARTICLES CRITICALLY APPRAISED

Botez-Marquard, T. & Botez, M. I. (1993). Cognitive behavior in hereditary degenerative ataxias. *European Neurology* 33(5): 351-357.

Hart, R. P., Kwentus, J. A., Leshner, R. T. et al. (1985). Information processing speed in Friedreich's ataxia. *Annals of Neurology* 17(6): 612-614.

### ARTICLES EXCLUDED FROM CRITICAL APPRAISAL

#### Descriptive Case Reports (Level IV evidence)

Mielke, R., Hilker, R., Weber-Luxenburger, G. et al. (1998). Early-onset cerebellar ataxia (EOCA) with retained reflexes: reduced cerebellar benzodiazepine-receptor binding, progressive metabolic and cognitive impairment. *Movement Disorders* 13(4): 739-745.

#### Non-English articles

Ayuso Mateos, J. L., Bayon, C., Santo-Domingo, J. et al. (1997). [Psychiatric disorders and cognitive deterioration in Friedreich ataxia]. *Actas Luso-Espanolas de Neurologia, Psiquiatria y Ciencias Afines* 25(5): 291-294.

Cisneros, E. & Braun, C. M. (1995). [Vocal and respiratory diadochokinesia in Friedreich's ataxia. Neuropathological correlations]. *Revue Neurologique* 151(2): 113-123.

# APPENDIX 1

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## Levels of Evidence

Based on "How to use the evidence: assessment and application of scientific evidence" (National Health & Medical Research Council, Canberra, 2000):

Level I		Evidence obtained from a systematic review (or meta-analysis) of all relevant randomised controlled trials.
Level II		Evidence obtained from at least one randomised controlled trial.
Level III	-1	Evidence obtained from pseudorandomised controlled trials (alternate allocation or some other method).
	-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case control studies or interrupted time series with a control group.
	-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
Level IV		Evidence obtained from case series, either post-test or pretest/post-test.

## APPENDIX 2

### Search strategy

	Search terms for MEDLINE, PREMEDLINE, CINAHL, Current Contents, PsycINFO, SocioFile
1	Friedreich ataxia/
2	(Fried\$ adj ataxia).mp
3	exp Cognition Disorders/
4	(cognit\$ adj disorder\$.mp
5	(cognit\$ adj impair\$.mp
6	(cognit\$ adj deficit\$.mp
7	or/1-2
8	or/3-6
9	7 and 8

\$ = wildcard indicating truncation

<p style="text-align: center;"><b>Evidence Summary</b> <b>Aetiology</b></p> <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: fit-content;"> <p>Cognitive changes associated with Friedreich's ataxia</p> </div>	<p style="text-align: center;">Botez-Marquard, T. &amp; Botez, M. I. (1993). Cognitive behavior in hereditodegenerative ataxias. <i>European Neurology</i> 33(5): 351-357.</p>
<p><b>STUDY DESIGN &amp; NHMRC LEVELS OF EVIDENCE</b></p>	<p>Case-control study Level III-2</p>
<p><b>DESCRIPTION:</b> Patients (subjects), Exposure, Comparisons, Outcomes, Inclusion &amp; Exclusion Criteria</p>	<p><b>Patients (subjects):</b> presenting at one hospital in Montreal, Canada  <b>Exposure:</b> Friedreich's ataxia (FA), <i>n</i>=15 patients, with well-delimited cerebellar damage  <b>Comparisons:</b> 15 normal controls matched for age, sex and education  <b>Outcomes:</b> neuropsychological test battery: information processing speed (IPS) by measuring visual and auditory reaction time (VRT and ART) and visual and auditory movement time (VMT and AMT), general intelligence via Raven's standard progressive matrices (RSPM), parts of Ottawa-Wechsler IQ scale to assess verbal and non-verbal acquired abilities, Rey auditory-verbal learning test.  <b>Inclusion &amp; Exclusion Criteria:</b> Exclusions: FA and OPCA patients with central and cortical atrophies according to radiological criteria, alcoholics, epileptics, psychiatric patients and those with severe articulatory disorders precluding neuropsychological assessment, those with corrected visual acuity &lt;5/10 in one eye or oculomotor disturbances, patients with severe depression or severe motor disturbances in either hand (assessed by grip strength).</p>
<p><b>VALIDITY:</b> Methodology, rigour, selection</p>	<p><b>Similar groups:</b> Normal controls were similar to FA group on average for age, sex, level of education, and socio-economic background.  <b>Consistent/objective measure of exposure:</b> FA diagnosed by criteria of Harding and cerebellar damage assessed by CT. These tests were not applied to the control patients.  <b>Objective or blinded measure of outcomes:</b> not possible to blind 'exposure' (i.e. not possible to mask whether patient had FA or not)  <b>Correct temporal relationship:</b> not addressed  <b>Dose-response gradient:</b> not addressed, patients in FA group had similar deficiencies</p>
<p><b>RESULTS:</b> Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p><b>IPS:</b> VRT, ART, VMT, AMT were delayed in the FA group compared to controls  <b>Intelligence:</b> FA group performed worse in the RSPM  <b>Rey test:</b> FA group displayed quantitative and qualitative impairments compared to controls</p>
<p><b>AUTHOR(S) CONCLUSIONS:</b> Limitations, implications for practice and research</p>	<p>Cognition was slowed and simple visual and auditory reaction times were delayed in the FA group compared to controls. This may be indicative of a role of the cerebellum in speed of information processing and cognition.</p>
<p><b>OUR COMMENTS:</b> Opportunity for bias, weaknesses and strengths</p>	<p><b>Potential for bias:</b> Control group matched FA group on average, but details of how controls were chosen and matched were scarce. Control group did not undergo CT scan or diagnostic test to assess any brain damage  <b>Strength/s:</b> Level III-2 is a highest possible level to investigate a study of this type (i.e. it is not possible to randomly assign patients to Friedreich's ataxia or normal control)</p>

<p style="text-align: center;"><b>Evidence Summary Aetiology</b></p> <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: fit-content;"> <p>Cognitive changes associated with Friedreich's ataxia</p> </div>	<p style="text-align: center;">Hart, R. P., Kwentus, J. A., Leshner, R. T. <i>et al.</i> (1985). Information processing speed in Friedreich's ataxia. <i>Annals of Neurology</i> 17(6): 612-614.</p>
<p><b>STUDY DESIGN &amp; NHMRC LEVELS OF EVIDENCE</b></p>	<p>Case-control study Level III-2</p>
<p><b>DESCRIPTION:</b> Patients (subjects), Exposure, Comparisons, Outcomes, Inclusion &amp; Exclusion Criteria</p>	<p><b>Patients (subjects):</b> convenience sample? Not stated where they were selected from <b>Exposure:</b> Friedreich's ataxia (FA), <i>n</i>=3 <b>Comparisons:</b> <i>n</i>=6 normal controls, matched by vocabulary and information scores on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) <b>Outcomes:</b> short-term memory scanning procedure, the vocabulary and information sections of the WAIS-R, an auditory vigilance test, the logical memory portion of the Wechsler Memory Scale, the Categories Test, a facial recognition memory test, a verbal learning task <b>Inclusion &amp; Exclusion Criteria:</b> not stated</p>
<p><b>VALIDITY:</b> Methodology, rigour, selection</p>	<p><b>Similar groups:</b> groups matched for vocabulary and information scores on the WAIS-R, not stated if matched for other variables <b>Consistent/objective measure of exposure:</b> FA assessed by the Inherited Ataxias Progression Scale, this scale did not appear to be applied to the control group <b>Objective or blinded measure of outcomes:</b> not possible to blind outcome assessors to presence of FA. It is not clear whether outcome measures used are well-validated objective measures <b>Correct temporal relationship:</b> not addressed <b>Dose-response gradient:</b> not addressed</p>
<p><b>RESULTS:</b> Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>FA patients demonstrated a deficit in information processing speed in the relative absence of impairment in attention, memory, language, judgement, reasoning, and other cognitive functions.</p>
<p><b>AUTHOR(S) CONCLUSIONS:</b> Limitations, implications for practice and research</p>	<p>'...the present finding should be replicated with a larger number of subjects. The short-term memory scanning procedure may be useful in documenting cognitive slowing in neurological disorders involving abnormalities of subcortical brain and in distinguishing this impairment from motor abnormalities'.</p>
<p><b>OUR COMMENTS:</b> Opportunity for bias, weaknesses and strengths</p>	<p><b>Potential for bias:</b> May be subject to selection bias because controls were matched on one of the outcome measures and there is no information about how they were selected. It is possible that controls were selected after the outcomes were measured rather than selected consecutively. Controls did not appear to be matched on factors such as age, education, socio-economic status, etc. Small study. <b>Strength/s:</b> A level III-2 study is a highest possible study design to investigate a study of this type</p>

## EXPLANATION OF TERMINOLOGY USED IN SPREADSHEET

**Aetiology:** Examines an association between exposure to a disease/therapy/environmental exposure and an outcome or adverse event.

**Level of evidence:** A hierarchy of study evidence that indicates the degree to which bias has been eliminated in the study design.

**Exposure:** Treatment, disease state, environmental exposure that is under suspicion of being associated with the outcome of interest (e.g. exposure: smoking, outcome: lung cancer).

**Blinding:** Blinding or masking is a process used in epidemiological studies and clinical trials in which the observers and the subjects have no knowledge as to which exposure group subjects are in. It is undertaken in order to minimise bias occurring in patient response and outcome measurement.

**Patients treated equally:** To be able to attribute any difference in the observed outcome to the intervention, study patients need to be treated equally in every way except for the intervention being evaluated.

**Similar groups:** Baseline characteristics of patients that are also likely to affect results (confounders) should be evenly distributed between the exposure and control groups. If not, statistical procedures should be used to account for imbalances between groups.

**Validity:** Of study: the degree to which the inferences drawn from the study are warranted when account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn (internal and external validity, applicability, generalisability).

**Potential for bias:** Bias is a systematic deviation of a measurement from the 'true' value leading to either an over (or under) estimation of the treatment effect. Bias can originate from many different sources (including patient selection, measurement, interpretation, publication and review of data).

**Correct temporal relationship:** The study should take steps to be as sure as possible that exposure preceded the onset of the outcome of interest in the patient group.

**Dose-response gradient:** A demonstration of an increased risk or severity of the outcome/adverse event with increasing exposure (increased dose and/or duration of exposure)