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TITLE: Profile of the Neurofibromatosis Type 1 (NF1) Phenotype: Natural History, Neuropsychological and Psychosocial Aspects

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### Title and Subtitle
Profile of the Neurofibromatosis Type 1 (NF1) Phenotype: Natural History, Neuropsychological and Psychosocial Aspects

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### Abstract
The natural history of both cognitive functioning and T2-hyperintensities is being examined in a longitudinal study of a cohort of 32 patients with NF1 and 11 controls. Follow-up neuropsychological assessments and cranial MRIs were performed after an 8-year period. Preliminary data analysis suggests that there is no improvement in cognitive function over time. MRI T2-hyperintensities decrease in size, intensity and number over time. However lesions in the basal ganglia behave differently from lesions in the cortex and brainstem, suggesting different underlying pathogenetic mechanisms. The timing of the MRI scan appears important in terms of its ability to predict cognitive deficits.

In addition, we are conducting a comprehensive neuropsychological study of a cohort of 80 children with NF1 and 50 sibling controls. Patient ascertainment and testing is still in progress. These children (8-16 years) will undergo intensive cognitive assessments and MRIs. The relationship between T2-hyperintensities on cranial MRI and neuropsychological functioning will be examined by determining whether the number, size, or sites of these lesions are predictive of general or specific neuropsychological deficits.

A multicentre study is also being conducted to characterise the distribution of IQ scores in a large international cohort of patients with NF1 and to determine whether any clinical or demographic variables are associated with lowering of IQ.
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ANNUAL PROGRESS REPORT

Introduction
Study 1 is a longitudinal study of a cohort of 32 patients with NF1 and 11 controls. Follow-up neuropsychological assessments and cranial MRIs have been performed after an 8-year period to determine the natural history of cognitive functioning and T2-hyperintensities. We also determined whether changes in T2-hyperintensities are predictive of changes in neuropsychological abilities.

Study 2 is a cohort study examining 80 children with NF1 and 50 sibling controls. These children (8-16 years) will undergo cognitive assessments, to develop a comprehensive neuropsychological and psychosocial profile. In addition, the relationship between T2-hyperintensities on cranial MRI and neuropsychological functioning will be examined to determine whether the number, size, or sites of these lesions are predictive of general or specific neuropsychological deficits.

Study 3 is a multicentre study which will characterise the distribution of IQ scores in a large international cohort of patients with NF1. We will determine whether any clinical or demographic variables are associated with lowering of IQ.

Body

Study 1
We have recruited and tested a total of 44 participants which include 33 patients with NF1 and 11 without NF1. From the original 40 patients with NF1, 2 have been excluded according to the exclusion criteria. 33 patients have agreed to participate. One patient with NF1 has been diagnosed with a brain tumour and will be excluded from analysis. We have had difficulty contacting the remaining 5 patients since they have moved interstate and been lost to follow up. We will try and recruit them if they return for a clinic visit. However it is likely that we have now completed subject ascertainment for this part of the study. Of the 14 control siblings, 11 have participated, 2 have refused to participate, and 1 patient cannot be located.

All patients and controls have undergone all aspects of testing, that is, a psychometric assessment and an MRI. Since data analysis is still in progress, we cannot yet state firm conclusions. However initial data analysis suggests the following findings of clinical significance:

1. When changes over time in patients with NF1 are compared to controls there are no significant differences between groups in:
   - general intellectual functioning
   - verbal reasoning skills
   - nonverbal reasoning skills
   - problem solving skills
   - verbal fluency
   - visuospatial skills

---

1 These patients were followed-up from a study conducted in 1992 (North et al, 1994: North et al, 1995). This study had 40 patients with NF1 and 14 controls, however not all subjects were able to be followed-up.
This is the first longitudinal study of cognitive function in NF1. Previous studies, based on cross-sectional data have suggested that there is an improvement in cognitive function over time in patients with NF1. Our results do not support this.

**Figure 1: Natural History of Full Scale IQ (FSIQ) in NF1**

**Figure 2: Comparison of Total Lesion Load Score**

To analyse the MRI findings and the natural history of T2-hyperintensities we have developed a new classification system (Lesion Load score).

**Classification of T2-hyperintensities**

Size: 1 (<5mm), 2 (6-10mm), 3 (11mm+)

Intensity: 1 (diffuse, low intensity),
2 (discrete lesion, low-moderate intensity)
3 (discrete lesion, high intensity)

*Lesion load score = size (1-3) + intensity (2 or 3)*

**Results to date:**

<table>
<thead>
<tr>
<th></th>
<th>1992</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with T2+</td>
<td>63%</td>
<td>44%</td>
</tr>
<tr>
<td>Lesion load score (LLS)</td>
<td>216</td>
<td>93</td>
</tr>
<tr>
<td>Mean LLS</td>
<td>8</td>
<td>3.4</td>
</tr>
</tbody>
</table>

1992 - 17 patients with T2-hyperintensities
2000 - lesions ↓ in no. and intensity in 15 patients
       - remained the same in one patient
       - increased in one patient
       - only one patient (T2- in 1992) developed T2+
1992 - 50% of T2-hyperintensities in basal ganglia
2000 - 56% disappeared completely and the remainder decreased in size, intensity or both

1992 - 10 brainstem T2-hyperintensities
2000 - 8 disappeared
  - 1 ↓intensity, same size
  - 1 ↓intensity, increase size

None of the cortical lesions disappeared from 1992-2000. In 2000, 50% of all T2-hyperintensities in cortex.

2000 - 14 new lesions - 8 in cortex, 2 in brainstem, 2 in thalamus, 2 in corpus callosum.
No new basal ganglia T2-hyperintensities

Study 2
From the total of 80 patients with NF1 and 50 sibling controls that will be recruited, 57 participants have been recruited, 39 with NF1 & 18 unaffected siblings. All these patients have undergone both neuropsychological/psychosocial assessment sessions and an MRI. Certain patients (depending on the timing of their last medical check-up) have also had medical assessments. Patient ascertainment and testing is still to be completed.

Study 3
Seven centres have agreed to participate. Each centre has sent the de-identified data to Australia (i.e. they have provided IQ, clinical and MRI data identified only as Patient #1, Patient #2...etc). The data not yet been examined. No results are available.
Key Research Accomplishments

Study 1
♦ From the previous cohort of 40 patients with NF1 and 14 controls, 33 patients with NF1 and 11 controls have been recruited and have undergone a follow-up neuropsychological assessment. Those with NF1 have also had a follow-up cranial MRI.
♦ This is the first prospective longitudinal study of cognitive function and MRIs in patients with NF1. Initial data analysis suggests that there is no improvement in cognitive function over time and that there is a significant decrease in T2-hyperintensities in the basal ganglia over time – but not in other regions of the brain. Thus it is likely that different pathogenetic mechanisms underlie the presence of T2-hyperintensities in different parts of the brain. In study 2, we will thus analyse all T2-hyperintensities relative to cognitive function and then analyse the basal ganglia lesions separately to determine if they have a separate effect on cognitive phenotype.
♦ Preliminary analysis (still incomplete) suggests there is no association between individual changes in any neuropsychological abilities and T2-hyperintensities when . It is also likely that the presence of T2-hyperintensities in the 1992 scan, compared to the 2000 scan, is a better predictor of neuropsychological ability in 2000. i.e. the timing of the MRI is an important variable in studies examining the association between T2-hyperintensities and cognitive function

Study 2
♦ 39 patients with NF1 and 18 unaffected sibling controls have all undergone 2 neuropsychological and psychosocial assessment sessions. The patients with NF1 have had a cranial MRI.
♦ The study design for Study 2 directly addresses the weaknesses of previous studies and thus our results will be able to address controversies concerning the cognitive phenotype, the incidence of ADHD in NF1 and the association between T2-hyperintensities and cognitive functioning.

Design Strengths: Large sample size
♦ Inclusion of sibling controls
♦ Use of co-normed test for assessing SLD (WIAT)
♦ Analysis of types of attentional difficulties
♦ In depth analysis of perceptual skills
♦ New tests of executive functioning (CCT & BRIEF)
♦ Examination of visual memory, controlling for perceptual difficulties.
♦ Examination of real-world (functional) correlates of perceptual, attention and executive dysfunction

Study 3
♦ 7 centres have been contacted and have sent their de-idenitified data to Australia.

Reportable Outcomes

Data analysis is still incomplete with findings as listed above from the Natural History study. Preliminary data analysis from Study 1 suggests that there is no improvement
in cognitive function over time in patients with NF1. MRI T2-hyperintensities decrease in size, intensity and number over time. However lesions in the basal ganglia behave differently from lesions in the cortex and brainstem, suggesting different underlying pathogenetic mechanisms. The timing of the MRI scan appears important in terms of its ability to predict cognitive deficits. These results will have clinical relevance in terms of timing of intervention for cognitive deficits, as well as research implications for the analysis of data correlating MRI lesions with the cognitive phenotype. As a direct result of our initial results from Study 1, we will analyse basal ganglia lesions as a separate variable (in Study 2) to determine their association with specific neuropsychological deficits.

We envisage that there will be 2 manuscripts arising from Study 1 (these should be completed by end 2001), at least 2 from Study 2 and one from Study 3 (by end of funding period). Associate Professor North will present some of the preliminary data at the Neurofibromatosis Symposium being held in conjunction with the Child Neurology Society meeting in Victoria BC in October, 2001

**Conclusions**

We are on track with our research plan as outlined in the Timeline and Statement of Work (appendix A). We have had no problems with patient ascertainment and will achieve the aims of the study as outlined in the grant proposal. Our preliminary analysis of the natural history data has already yielded important information that specifically addresses controversies within the literature, and is likely to have clinical relevance.

**References**


**Appendices**

Appendix A – Statement of Work and Timeline of Project
Appendix B – Ethic approval for revisions requested by USAMRMC
**STATEMENT OF WORK – Revised 25th May 2001**
(for timeline refer to the chart on the next page)

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Prospective longitudinal study of our original cohort of 50 patients (0-18 months).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>re-assessment of original cohort (medical, cognitive function, MRI); re-analyse using previous statistical techniques; developmental (natural history) comparison of changes in UBO status and intelligence.</td>
</tr>
<tr>
<td>Sample</td>
<td>40 NF1 patients in original cohort; aged now 15-25 years; approximately equal distribution by sex.</td>
</tr>
<tr>
<td>Deliverables</td>
<td>confirmation or rejection of the correlation between number of UBOs, age and intelligence, progress report, two journal articles.</td>
</tr>
<tr>
<td>Funding</td>
<td>National Neurofibromatosis Foundation (first 12 months only) + USAMRMC (12-18 months)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study 2</th>
<th>1. Replication of our initial study in a new cohort of 80 children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Control study - using unaffected siblings (12-36 months)</td>
</tr>
<tr>
<td>Methods</td>
<td>neuropsychological and psychosocial assessment of new cohort and sibling controls</td>
</tr>
<tr>
<td>Previous data</td>
<td>comparative data from the 1992 study.</td>
</tr>
<tr>
<td>Sample</td>
<td>80 NF1 patients, aged 8-16 years ascertained sequentially; excluding patients with intracranial pathology, IQ &lt; 70 and currently on medication that could affect test performance; and 50 non-NF1-affected siblings, aged over 6 years and preferably &lt;18 years.</td>
</tr>
<tr>
<td>Deliverables</td>
<td>confirmation or rejection of previous findings; extension of the study to increase rigor, reliability and statistical power; control for familial factors in phenotype; progress report, two journal articles.</td>
</tr>
<tr>
<td>Funding</td>
<td>USAMRMC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study 3</th>
<th>International collaborative study of over 700 patients with NF1 (18-36 months).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>collect data on NF1 studies from Ferner (UK), Riccardi (USA), Legius (Belgium), Samango-Sprouse (USA), Tenconi (Italy), Sadeh (Israel) and combine with our studies (North; Australia) as produced by the researchers above who are collaborating in this part of the project; includes intelligence scores, JLO, VMI, Achenbach, and academic achievement.</td>
</tr>
<tr>
<td>Previous data</td>
<td>patients with NF1; children, adolescents and adults; male and female; multi-ethnic.</td>
</tr>
<tr>
<td>Sample</td>
<td>theoretical advances in understanding the cognitive phenotype of NF1 patients, particularly, data on distribution of intelligence, progress report, one journal article.</td>
</tr>
<tr>
<td>Funding</td>
<td>USAMRMC</td>
</tr>
</tbody>
</table>
Timeline for Studies involving NF 1 Patients

<table>
<thead>
<tr>
<th>Study 1 (Natural History)</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. contact all patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. re-assess medically</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. re-perform cranial MRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. re-assess cognitive function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. re-assess academic achievement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. enter and analyze data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. write up</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study 2 (Replication and Extension)

New Cohort Replication
1. contact all patients
2. assess medically
3. perform cranial MRI
4. assess cognitive function
5. assess academic achievement
6. enter and analyze data
7. write up

Non-NF1 Siblings Comparison
1. contact all patients
2. assess cognitive function
3. assess academic achievement
4. enter and analyze data
5. write up

Project Management and Publications
1. debrief participants
2. prepare project reports for funder
3. prepare and submit journal articles
4. finalize all financial acquittals

Study 3 – International Extension
1. Collect data
2. Analyse data
3. Write up
27 June, 2001

A/Prof Kathy North
Neurogenetics Research Unit

Dear A/Prof North,

Title: A prospective analysis of the NF1 phenotype:
natural history, pathogenesis and therapy

Project Number: 97002 (to be quoted in future correspondence)

Original Approval: 28th February 1997
Amendment Approval: 18th December 1998
Amendment Approval: 26th June 2001

Study 1 Natural history of the neurofibromatosis type 1
phenotype: neuropsychological and neuroradiological
aspects, and
Study 2 Profile of the NF1 cognitive phenotype:
neuropsychological and psychosocial aspects

This is to confirm that final approval has been granted for this study. All the
requirements of the Ethics Committee are satisfied and your approval is valid.

We wish you well with your study. Please contact me if you have any further questions.

Yours sincerely,

[Signature]
A O'Neill
Secretary, Ethics Committee
A Prof K North  
Neurogenetics Research

Dear A/Prof North,

A prospective analysis of the NF1 phenotype: natural history, pathogenesis and therapy  
97002  
(Variation dated: 26 June 2001)

At its meeting on 24 August 2001, the Ethics Committee approved amendments to this project.

We wish you well with your project. Please contact us should you have any queries.

Yours sincerely,

A O'Neill  
Secretary, Ethics Committee