Neuropsychological tests and functional nuclear neuroimaging provide evidence of subclinical impairment in Nasu-Hakola disease heterozygotes

Lorenza Montalbetti
Maria Teresa Ratti
Bianca Greco
Carlo Aprile
Arrigo Moglia
Debora Soragna

a Department of Neuroscience, University of Pavia, IRCCS C. Mondino Institute of Neurology, Pavia, Italy
b IRCCS C. Mondino Institute of Neurology, Pavia, Italy
c Department of Nuclear Medicine, IRCCS S. Maugeri Foundation, Pavia, Italy
d Department of General Biology and Medical Genetics, University of Pavia, Italy

Reprint requests to: Prof. Lorenza Montalbetti
Department of Neuroscience, University of Pavia
IRCCS “C. Mondino” Institute of Neurology
Via Mondino, 2 - 27100 Pavia - Italy
E mail: lmontalb@unipv.it

Accepted for publication: February 7, 2005

Summary

Nasu-Hakola disease is a rare, recessively inherited disease characterized by presenile dementia and bone cysts. Until now, no evidence of subclinical pathological changes in individuals heterozygous for the mutations underlying Nasu-Hakola disease has been reported. We performed a functional neuroimaging (99mTc-ECD SPECT) and neuropsychological study of healthy members of an Italian family carrying a mutation in the TREM2 gene. Two healthy subjects heterozygous for one mutated TREM2 allele showed a deficit of visuo-spatial memory associated with hypoperfusion in the basal ganglia, whereas the homozygotes for the wild-type allele of TREM2 did not show any abnormalities.

KEYWORDS: cognition, heterozygotes, Nasu-Hakola disease, neuropsychological tests, SPECT.

Introduction

Nasu-Hakola disease (polycystic lipomembranous osteodysplasia with sclerosing leuкоencephalopathy, PLOSL; MIM 221770) is a rare, recessively inherited disease characterized by progressive presenile dementia associated with sclerosing leuкоencephalopathy and systemic bone cysts (1,2). Neuropsychiatric symptoms appear insidiously and gradually evolve into a prefrontal syndrome, which leads to severe global cognitive impairment. Neuroradiological findings show cerebral atrophy and diffuse white matter abnormalities, more prominent in the frontal lobes, associated with calcifications of the basal ganglia. Brain pathology is characterized by loss of myelin and of nerve fibres and gliosis accentuated in the frontal region (1). A positron emission tomography (PET) study of cerebral glucose metabolism (3) detected hypofunction of the frontal lobes and basal ganglia, predominant in the right hemisphere. PLOSL is characterized by genetic heterogeneity: mutations in two genes (TYROBP and TREM2), which encode two different subunits of a membrane receptor complex in natural killer and myeloid cells, have been associated with the disease (4,5). Although the signalling pathway responsible for PLOSL has been identified and there is some experimental evidence of its role in signal transduction, bone modelling and brain myelination, the pathogenesis of Nasu-Hakola disease is still unclear (4).

Until now, little attention has been paid to possible minor manifestations – such as microcystic lesions of the tarsal and carpal bones, focal epilepsy, and electroencephalographic abnormalities (6) – in Nasu-Hakola disease heterozygotes, and the specificity and importance of these findings remain to be established.

In order to identify some subclinical features of Nasu-Hakola disease heterozygotes, we performed a comprehensive neuropsychological assessment and a single positron emission computer tomography (SPECT) evaluation in members of an Italian family with a novel mutation in exon 2 of the TREM2 gene (97C→T; Q33X) (5).

Materials and methods

The clinical and genetic analyses performed were described previously (5) and family pedigree is shown in figure 1 (over). Subjects II,2, II,3, II,4, and III,1 were submitted to a battery of neuropsychological tests covering a wide range of cognitive functions. The battery included tests of logical abilities (Raven Progressive Matrices PM’38: IQ) (7,8), selective attention (Attention Matrices Test) (9), language abilities and frontal functions (Verbal Fluency: phonetic and semantic cues) (10-12), verbal memory (Forward Digit Span, Story Recall, Learning Three Lists of Words) (13,14), and visuo-spatial memory (Corsi’s Block Tapping Test: Spatial Span and Spatial Supra-Span (9,15), Rey-Osterrieth Complex Figure Test (16)). Individual II,1 was not tested since she already showed cognitive impairment. Raw scores on all tests were converted into scores ad-
justed for age and educational level and into intelligence quotient (IQ) on the basis of Raven’s Progressive Matrices. Adjusted scores on the Attention Matrices Test, Story Recall, Learning Three Lists of Words, Spatial Span and Supra-Span, Recall of Rey-Osterrieth Complex Figure Test and Verbal Fluency tests were converted into equivalent scores using a new 0-4 scale (in which 0 corresponds to a score below the 5% tolerance limits, 4 corresponds to a score equal to or better than the mean, and 1-2-3 correspond to intermediate scores between 0 and 4). This conversion was possible because equivalent scores were calculated during the standardization of the test (9,15,16).

A patient’s performance on any test was considered abnormal when the score achieved fell below a cut-off point corresponding to the worst score recorded by at least 95% of the population.

In subjects II,1, II,2, II,3, II,4, and III,1 a SPECT study of regional cerebral perfusion was performed using 99mTc-bis-dihydroxide dihydrochloride (99mTc-DPDP) as tracer, and using a double-head camera (Varicam-Millennium, GE Healthcare, UK) equipped with general purpose collimator. 99mTc-ECD was administered intravenously at a dose of 740 MBq (20mCi). After 45 minutes data were collected for 64 views of 25 sec, with angular step of 3°, in a 128x128 region, especially on the right side, associated with low cerebral perfusion with marked hypoperfusion in the right basal ganglia region, especially on the right side, associated with low cerebral perfusion with marked hypoperfusion in the right basal ganglia, more prevalent in the right and in the frontal and parieto-occipital cortex (Fig. 2).

Scores obtained on Verbal Fluency tests were normal, but the patient produced neologisms. She showed a severe deterioration of intellectual functions (IQ=60). The patient also presented dyscalculia and dysgraphia. At the same time, a SPECT study of cerebral perfusion with 99mTc-ECD showed moderate hypoperfusion in the right basal ganglia and right frontal cortex. At the age of 37 years, she presented a global worsening of neuropsychological functions, which made neuropsychological reassessment impossible. SPECT revealed a worsening of cerebral perfusion with marked hypoperfusion in the basal ganglia, more prevalent in the right and in the frontal and parieto-occipital cortex (Fig. 2).

Case II,1 (affected sister of II,2) was submitted to neuropsychological tests at the onset of her Nasu-Hakola disease (before the diagnosis had been formulated). The results of these tests were suggestive of frontal dysfunctions. Her personal history was characterized by multiple spontaneous fractures of the extremities and X-ray examination detected multiple bone cysts (5). When we observed the patient at the age of 44 years, she presented severe impairment of cognitive and motor functions, which made neuropsychological assessment impossible. At that time, brain SPECT with 99mTc-ECD showed marked hypoperfusion of the basal ganglia region, especially on the right side, associated with low tracer uptake in bilateral frontal regions. The third sister (II,3) was healthy and homozygous for the wild-type allele. At the age of 41 years, neuropsychological tests at the onset of her Nasu-Hakola disease were normal for verbal material and no confabulations were found. A weakness of visuo-spatial short-term memory was suggested by her poor performance on Spatial Span and impairment of visuo-spatial long-term memory was found on Spatial Supra-Span. She was unable to perform Rey-Osterrieth Complex Figure: recall (Table I).

Results

Patient II,2 is a 37-year-old female affected by PLOSL, homozygous for the mutation in exon 2 of the TREM2 gene (5). This patient’s clinical picture was characterized by a severe progressive dementia associated with radiological evidence of multiple cystic lesions in the metaphyseal regions of bones (5). At the age of 35 years she was submitted to neuropsychological evaluation. She was very talkative and euphoric and was very inclined to joke while undergoing the neuropsychological tests. The patient was completely oriented with respect to time and place but her attention was impaired. The capacity to acquire and retain new memory data was normal for verbal material and no confabulations were found. A weakness of visuo-spatial short-term memory was suggested by her poor performance on Spatial Span and impairment of visuo-spatial long-term memory was found on Spatial Supra-Span. She was unable to perform Rey-Osterrieth Complex Figure: recall (Table I).

Figure 1 - Pedigree of an Italian family affected by Nasu-Hakola disease with a novel mutation in the TREM2 gene. Black symbols denote affected individuals, white symbols denote unaffected individuals, and half black symbols denote carriers. *=individuals with visuo-spatial deficit; **=individuals with cerebral hypoperfusion.
I). Brain SPECT with $^{99m}$Tc-ECD was within normal limits (Fig. 2). The brother (II,4) was a heterozygous carrier of the mutated allele. On neuropsychological assessment at the age of 44 years, he presented a severe selective deficit of short- and long-term visuo-spatial memory (Table I). He was conscious of this deficit and maintained that it had appeared during childhood. At the time of that assessment, SPECT study indicated mild hypoperfusion in the right basal ganglia (Fig. 2).

### Table I - Results of neuropsychological assessments.

<table>
<thead>
<tr>
<th>Neuropsychological tests</th>
<th>Case II,2</th>
<th>Case II,3</th>
<th>Case II,4</th>
<th>Case III,1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(age 35 y, r.h., h.s, manager)</td>
<td>(age 41 y, r.h., h.s, manager)</td>
<td>(age 43 y, r.h., h.s, manager)</td>
<td>(20 y, r.h., student)</td>
</tr>
<tr>
<td>Raven's Progressive Matrices (IQ)</td>
<td>– 60*</td>
<td>– 125</td>
<td>– 110</td>
<td>– 123</td>
</tr>
<tr>
<td>Attention Matrices Test</td>
<td>27.75* 0*</td>
<td>58.0 4</td>
<td>45.25 3</td>
<td>43.0 3</td>
</tr>
<tr>
<td>Verbal Fluency: phonetic cues</td>
<td>19.0 1</td>
<td>27.0 3</td>
<td>44.0 4</td>
<td>30.0 3</td>
</tr>
<tr>
<td>semantic cues</td>
<td>28.0 1</td>
<td>46.0 4</td>
<td>58.0 4</td>
<td>35.0 3</td>
</tr>
<tr>
<td>Forward Digit Span</td>
<td>6.50 0</td>
<td>5.50 2</td>
<td>4.25 4</td>
<td>5.75 4</td>
</tr>
<tr>
<td>Story Recall</td>
<td>12.50 3</td>
<td>17.50 4</td>
<td>16.50 4</td>
<td>15.0 4</td>
</tr>
<tr>
<td>Learning Three Lists of Words</td>
<td>10.0 2</td>
<td>22.0 4</td>
<td>18.0 4</td>
<td>19.0 4</td>
</tr>
<tr>
<td>Corsi's Block Tapping Test: Spatial Span</td>
<td>3.75 1</td>
<td>4.75 2</td>
<td>1.50* 0*</td>
<td>2.50* 0*</td>
</tr>
<tr>
<td>Spatial Supra-Span</td>
<td>4.75* 0*</td>
<td>10.25 2</td>
<td>3.75* 0*</td>
<td>4.25* 0*</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure: recall</td>
<td>n.a. n.a.</td>
<td>12 2</td>
<td>8.50* 0*</td>
<td>9.45* 0*</td>
</tr>
</tbody>
</table>

Abbreviations: r.h.=right-handed; h.s.=educated to high school level; Ad=adjusted scores, Eq=equivalent scores, *=abnormal scores; n.a.=not administered.

Figure 2 - SPECT with $^{99m}$Tc-ECD. Cerebral perfusion in case II,2 (A), II,3 (B), and II,4 (C).
Individual III.1 was heterozygous for the mutated allele. At the age of 20 years, during neuropsychological assessment, she gave a better-than-average performance on Raven Progressive Matrices (IQ=123) and on verbal memory tests (Table I). She presented a selective deficit of short- and long-term visuo-spatial memory of which she was not aware. Brain SPECT revealed mild hypoperfusion in right basal ganglia.

X-ray examination of these three cases (II.3, II.4 and III.1) did not reveal bone abnormalities (5).

Discussion

The reported results may suggest that in Nasu-Hakola disease, heterozygotes show subclinical alterations involving specific brain regions, detectable with neuropsychological tests and SPECT. Heterozygotes for the mutated allele show impairment of visuo-spatial memory and mild hypoperfusion in the right basal ganglia. Homozygotes, in the first stage of the disease, present the same neuropsychological and neurofunctional patterns; in the subsequent stages, however, neuropsychological tests are no longer administrable and the hypoperfusion becomes severe and diffuse. Homozygotes for the wild-type allele, on the other hand, present normal neuropsychological and neuroimaging findings.

Given the limited number of cases available, these findings should be interpreted with caution. The hypometabolism observed with $^{99m}$Tc-ECD can be superimposed on that detected with PET study in another case of PLOSL (3). In that case (3), too, the decrease of regional cerebral glucose metabolism was observed predominantly in the right hemisphere, suggesting that right hemispheric dysfunction contributes to the peculiar behavioural abnormalities observed in PLOSL (3). Moreover, in our study the prevalence of the perfusion deficit in the right hemisphere seems to correlate with the visuo-spatial memory impairment detected on neuropsychological assessment (17), Ueki et al. (3) observed a decrease of cerebral metabolism in the basal ganglia and in the frontal white matter and suggested that the deficit of basal ganglia metabolism might be a secondary effect of primary frontal damage. On the contrary, in our study, the subclinical evidence of a selective metabolic deficit in the basal ganglia in the heterozygotes could indicate that basal ganglia are cerebral areas more susceptible to the alterations induced by the genetic defect and thus the first structures to be affected. Moreover, according to the model of cognitive control developed by Casey et al. (18), the basal ganglia can be regarded as structures involved in cognitive control and in inhibition of inappropriate behaviour.

Since the heterozygotes examined in this study are young, a follow-up investigation is warranted, not only to observe the evolution of the cerebral damage, but also to evaluate whether these subjects present a greater risk of comorbidty and of adverse effects of “normal” aging.

Further studies are required to establish the predictive value of these neuropsychological and neurofunctional changes.

Acknowledgments

We are grateful to the “Associazione Laura Fossati” Onlus, which supports clinical and genetic studies on Nasu-Hakola disease in Italy. Special thanks to Dr Ileana Ranzini for her valuable secretarial support.

References

