European Journal of Medical Genetics 57 (2014) 216–219

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Clinical report

Neuropsychological impairments in elderly Neurofibromatosis type 1 patients

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ARTICLE INFO

Article history:
Received 14 July 2013
Accepted 8 February 2014
Available online 18 February 2014

Keywords:
Aging
Cognition
Elderly
Neurofibromatosis type 1
Neuropsychology

ABSTRACT

Cognitive performance is compromised in Neurofibromatosis type 1 (NF1) patients, but neuropsychological data including elderly NF1 are extremely sparse. We compared the cognitive performance of a small elderly NF1 group ($n = 5$) with an age-matched healthy control group ($n = 49$). NF1 group performed worse than control group on a global cognitive impairment task, verbal working memory, and visuospatial functioning. The results suggest that cognitive impairment is an important feature of NF1 across lifespan, including elderly individuals. Future studies approaching the NF1 cognitive profile might benefit from looking at the mechanisms linked to the age-related aspects of cognitive decline.

1. Introduction

Neurofibromatosis type 1 (NF1) is a common autosomal disorder caused by dominant loss-of-function mutations of the tumor-suppressor gene NF1 (chromosome 17q11.2 in humans) [Carey et al., 1986]. NF1 main clinical features include multiple café-au-lait spots, axillary freckling, Lisch nodules, optic pathway gliomas, and cognitive deficits [Pasmant et al., 2012]. Despite marked phenotype expression variability, up to 70% of NF1 children have learning problems [Hyman et al., 2005] that are considered a significant source of decreased quality of life in NF1 [North et al., 1997].

NF1 patients usually present low-to-normal global intellectual functioning (90 IQ points in average) with a higher incidence of Intellectual Disability (6–7%) [Hyman et al., 2005]. Visuospatial impairment has long been documented as the most consistent cognitive feature of the disorder [Schrimsher et al., 2003], and deficits in executive functions (e.g. working memory, set-shifting, and inhibitory control), processing speed, motor control, and language also occur [Hachon et al., 2011]. However, the mechanisms of cognitive performance in NF1 remain unclear. Areas of hyperintensity on magnetic resonance may be associated to NF1 cognitive deficits in childhood, yet hyperintensities could be reduced in NF1 individuals at young adulthood with no changes in cognitive impairments across development [Hyman et al., 2003]. The majority of studies so far only included children and adolescents [Lehtonen et al., 2013]. Neuropsychological data in NF1 adults still limited and controversial [Descheemaeker et al. 2012 Oct 24] and, to the best of our knowledge, there is no published report considering only elderly individuals with NF1. Nonetheless, the cognitive deficits observed in NF1 seem to be

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http://dx.doi.org/10.1016/j.ejmg.2014.02.004
1769-7212/

stable across the life, with no evidence of progressive decline [Hyman et al., 2005; Payne et al., 2010].

Mutations in the NF1 gene can cause alterations in Ras signaling pathway by inactivating Ras-GAPs [Gysin et al., 2011]. NF1 loss and Ras hyperactivation in oligodendrocytes induce defects in myelin [Mayes et al., 2013 Sep 11]. NF1 brain abnormalities include, besides focal areas of high signal intensity on T2-weighted in magnetic resonance imaging (MRI), increased brain water diffusion in MRI, macrocephaly with higher white matter volumes, and larger corpus callosum [Payne et al., 2010]. Thus, there are converging evidences for impaired communication between different neural regions by early myelin dysfunction in NF1 [Gutmann et al., 1997].

In typical developing individuals, the late-myelinating regions (e.g. frontal lobe white matter, and genu of the corpus callosum) are more vulnerable to age-related myelin breakdown which might be one of the main mechanisms for cognitive decline in the healthy population [Lu et al., 2013]. Processes altering functional connectivity are involved in the age-related cognitive development of fine perceptual discriminations (mainly in the visual domain), in episodic memory tasks, working memory, executive functions (inhibition, and task-switching), and processing speed [Goh, 2011]. Therefore, NF1 population and typical elderly individuals may share brain and cognitive changes.

Even though NF1 cognitive deficits seem to be stable across life [Lehtonen et al., 2013], it is possible that early NF1 cognitive profile mimics age-related aspects of cognitive decline. However, the decreased cognitive performance in typical individuals will only be detectable in old age as a consequence of brain changes in aging. Thus, differently from studies including children, elderly NF1 individuals would present a less impacted cognitive profile compared to healthy controls. In this report, we investigated the cognitive performance of a rare group of elderly NF1 patients.

2. Clinical report

This was a case–control study involving five NF1 patients (diagnosed by the NIH criteria accomplishing a multidisciplinary assessment) [Gutmann et al., 2012] and 49 healthy controls matched in terms of age, formal education and gender to NF1 patients. Due to the expected high heterogeneity of NF1 patients' cognitive performance, we adopted a larger proportion of case and controls (1:~10). All participants had the Mini-Mental State Examination (MMSE) score above the Brazilian cut-off values for cognitive impairment based on education, although it was not an inclusion for the NF1 group [Castro-Costa et al., 2008]. Other inclusion criteria were: no evidence of functional impairment, history of neurologic or psychiatric disorders, alcohol or other substance abuse, or use of medication with known effects on cognitive functioning. From a total of 197 NF1 patients registered in the clinic database, 25 (13%) had 60 years or more. Seventeen older adults could not be contacted or could not attend (wrong phone number, older adults with residence on other cities or could not be contacted by phone). Three patients refused the invitation and five were willing to participate. The study was in accordance with the Helsinki declaration and was approved by the local institution ethics board.

The participants underwent neuropsychological assessment conducted by certified clinical neuropsychologists (DSC and JJP), using a comprehensive protocol designed for the assessment of older adults with low formal education. We assess the Executive functions by a Brazilian version of the Frontal Assessment Battery [de Paula et al., 2013], and the Inhibition and Shifting components of the Five Digits Test (FDT), a numeric-stroop task [de Paula et al., 2012a]. The executive scores of this second test (controlled process time − automatic process time) were adopted. Working memory was assessed by the Digit Span and the Corsi Span tasks [de Paula et al., 2013]. We used the maximum span achieved on the forward and backward orders on the study. For the evaluation of visuospatial abilities the 10-point scale of the MMSE Pentagons, we used the Stick Design Test [Baiyewu et al., 2005] and the Shulman Clock Drawing Test [de Paula et al., 2010]. For language and semantic memory two category fluency tests ("Animals" and "Supermarket"), the TN-LIN − a Brazilian naming test developed for the assessment of children and older adults with low formal education [Malloy-Diniz et al., 2007], and the short version of the Token Test [de Paula et al., 2010]. We assessed Processing Speed by the Reading and Counting Time of the FDT. Finally, episodic memory (learning, storage, and recollection) was investigated by the Brazilian-Portuguese version of the Rey Auditory-Verbal Learning Test [de Paula et al., 2012b].

The groups were compared by chi-square tests on categorical measures and the non-parametric test of Mann–Whitney on continuous measures. We adopted a more conservative value of statistical significance ($p = 0.01$) to avoid Type I errors due to multiple comparisons. Effect sizes were estimated by the r statistic ($r = Z/\sqrt{n}$). The clinical description of participants is shown on Table 1. There were no differences regarding age, education, depressive symptoms and proportion of man and women (all $p > 0.05$). However, there were significant differences in the MMSE ($U = 28.0$, $p = 0.004$, $r = -0.39$). The group comparisons on neuropsychological measures are shown on Table 2. The NF1 elderly patients performed significantly worse than healthy controls only on a verbal working memory test, and a visuo-constructional praxis measure (Stick Design Test). Despite non-significant, we found moderate effect sizes for inhibitory control measure, naming aspect of language/semantic memory, and on processing speed measures.

3. Discussion

To the best of our knowledge, this is the first study to assess specifically neuropsychological performance of older adults with NF1. We found that the NF1 group performed worse than the healthy group on a test of global cognitive impairment (Mini-Mental State Examination) with moderate effect size, although NF1 patients were not in the score range for clinical dementia. It is worth noting that IQ level has a predictive power on screening tests as MMSE [Alves et al., 2013 Jun]. This global cognitive difference is likely to reflect the NF1 mild intellectual inefficiency [Hyman et al., 2005]. Therefore, groups with low premorbid intelligence as NF1, have a higher risk to be misclassified as a result of inaccurate evaluation of premorbid cognitive features. Also, moderate

Table 1
Participants description.

Participants	Age	Education		Sex		MMSE[b]
		≥8 year	<8 year	Male	Female	
Patient 1	65	v	–	v	–	26
Patient 2	65	v	–	v	–	24
Patient 3	64	–	v	v	–	26
Patient 4	77	–	v	–	v	24
Patient 5	77	–	v	–	v	22
NF1	65 (3.03)[a]	51%	49%	25%	75%	24 (22–24)[a]
Controls	70 (0.93)[a]	40%	60%	60%	40%	29 (27–29)[a]

NF1: Neurofibromatosis Type 1, MMSE: Mini-Mental State Examination, GDS-15: Geriatric Depression Scale 15 items version.
[a] Expressed in median (Percentile 25 − Percentile 75).
[b] Significant group difference ($U = 28.0$, $p = 0.004$, $r = -0.39$).