Cognitive impairment and Fabry Disease: a case report with mutation S126G

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Abstract

Anderson-Fabry Disease is a lysosomal storage disease, multisystem, progressive, hereditary, linked to the X-chromosome. Specifically, it is characterized by a glycosphingolipid metabolism due to the reduction or absence of Alpha-galactosidase, an enzyme activity lisosomile gene mutation GLA (Xq21.3-q22), which encodes the enzyme. The decreased activity causes the accumulation of globotriaosylceramide (Gb3) within lysosomes, which in turn sets off a cascade of cellular events. The clinical picture presents a wide spectrum of manifestations of multiple systems: neurological, skin, kidney, cardiovascular disease, auditory and vestibular and cerebrovascular. Despite the recent interest in the involvement of cognitive studies in literature have not yet produced enough results to outline a possible neuropsychological profile of course. Also, not all researchers agree on the existence of a specific cognitive deficit of Fabry Disease (FD). The case discussed here is a example of a neuropsychological profile in patient with FD (mutation p.S126G).

Keywords: Fabry; Cognitive deficit; Stroke

1. Introduction

Fabry Disease (FD) is a multisystemic lysosomal storage disorder, inherited in X-linked manner (Colomba et al., 2015). It is caused by the functional deficit of α-galactosidase A (α-GAL A) (Brady et al., 1967), a lysosomal enzyme involved in the degradation of complex sphingolipids (mainly globotriaosylceramide). The total or partial deficit of this enzyme is responsible for the build-up of its substrates in different types of cells, like endothelial, renal, cardiac and nervous cells (Desnick, Ioannou & Eng, 2001; Germain, 2010). The α-GAL A is encoded by GLA gene, located on the long arm of X-chromosome (Xq21-22) (Kornreich, Desnick & Bishop, 1989), and the majority of mutations in this gene are associated to the FD. To date, about 790 alterations in the GLA gene were already described (Cooper et al., 2015). However, the involvement of some mutations in FD is still unclear, and many research teams in the world are performing studies in order to clarify these alterations.

Regarding the symptomatology, the first clinical manifestations occurs in the childhood with lancinating acroparesthesias, gastrointestinal pain associated with diarrhea alternated with sensation of abdominal fullness, *cornea verticillata*, fatigue, recurrent fever and headache. The angiokeratomas is one the typical manifestations of FD and they are localized mainly in the swimsuit area, even if patients with an giokeratomas *corporis diffusum* were described. Another typical feature of FD is hypohidrosis or anhidrosis that become critical elements in particular situation (like physical exercises and fever) in which the patient can manifest crisis of pain due to thermoregulation pathology. With the age, renal signs occur in patients such as proteinuria (Pisani et al., 2015). Moreover, patients can present lymphedemas mostly in the lower limbs. In the adulthood, many patients present an involvement of heart (frequently left ventricular hypertrophy) and kidney (leading to renal failure) (Colomba et al., 2015). Cerebrovascular impairment in FD subjects was described. Several epidemiologic studies in stroke patients were performed: in Germany, mutations in the GLA gene were found in the 4.9% of men and the 2.4% of women that were enrolled (Rolfs et al., 2005); the PORTYSTROKE study, performed in Portugal, showed a prevalence of 2.4% in this population (Baptista et al., 2010); in Italy, Romani et al. found GLA mutations in the 2.8% of analyzed patients with acute ischemic stroke or TIA (Romani et al., 2015). Another typical signs of FD is the tinnitus that was found in several FD individuals.

The symptomatology of FD can lead to the death of patient between the fourth and fifth decade of life. However, the typical clinical manifestations were described in patients with the severe form of FD (called classic

FD). Recently, many patients with atypical variant of FD were identified, which is characterized by an involvement of a single organ (Hoffmann & Mayatepek, 2009). Moreover, female FD patients manifest a milder and more variable symptomatology, since the FD is an X-linked disorder.

In recent years interest in the involvement of cognitive function in patients with FD is greatly increased. Nevertheless the studies in the literature have not yet clarified the existence of a link between the disease and cognitive deficits. "Question still remains open. Moreover the use of different instruments and mode selection, makes difficult the comparison among the few works present in the literature". Segal et al. (2010) studied 16 patients through intelligence tests, language, visual-spatial skills, memory and sensory-motor skills, attention and executive were tested with a computerized test battery, standard paper and pencil tests. Patients were screened for lifelong DSM-IV Axis-I and Axis-II. The results showed a normal pattern in most of the cognitive measures in patients with FD, even if the processing speed of the information and of the executive functions were subnormal. According to Segal (Segal et al., 2010), this preliminary study findings could shape a psychiatric and cognitive phenotype in patients AFD. We suggest that psychiatric and neuro-psychological evaluation be included in the patient's evaluation. A similar result was reported in the study of Elstein et al. (2012), in this case 10 patients were evaluated with a computerized battery (Mindstreams), while direct symptoms of FD were evaluated with MSSI (Mainz Severity Score Index) (Beck, 2006). The authors suggest that there is a pattern of cognitive impairment in FD, with major involvement of speed of information processing and the motor skills.

In a recent review (Bolsover, Murphy, Cipolotti, Werring & Lachmann, 2014) the authors suggest that FD may be associated with cognitive impairment and high prevalence of psychological disorders, characteristic pattern of deficits such as depression. The work highlights the limited data available emphasizing both the importance of neuropsychological research in FD and the limited results available in the literature. Also slight reductions in sustained attention processes were found by Schermuly et al. (2011), therefore the researchers conclude that in patients with FD, even those with marked structural alterations of the brain, show only mild cognitive impairment. While the high frequency of depression in FD is probably related to the weight of this hereditary chronic multiorgan disease, but not to the structural alterations FD-typical brain. Longitudinal studies are needed to clarify whether mild cognitive deficits in FD could precede any clinically significant cognitive decline (Schermuly et al., 2011). The study (Wadley et al., 2014) shows that the most significant sample involved 54 participants and 216 controls who were enrolled from September 2009 to May 2011 and evalu-

ated through a telephone interview. The study results suggest that methods of cognitive assessment based on the phone are feasible among the many patients with FD but do not show a significant difference in overall cognitive function between FD and control participants (Wadley et al., 2014). Furthermore Fellgiebel et al. (2012) reported in one study that patients with FD show a decrease of hippocampal volume which is not related to cognitive impairment, however the authors emphasize the need to monitor over time the cognitive functioning of patients with FD (Fellgiebel et al., 2012). The question remains open: there is a typical cognitive deficits of FD? Surely we will need more studies to clarify the matter. In this work we report a cognitive study of a case with mutation in the GLA gene that is still controversial if causes FD.

2. Case report

The patient is a 50 year-old woman with a history of recurrent carotid TIA, without receiving an etiological diagnosis. Moreover, she presented acroparesthesias, mild tinnitus, fatigue, proteinuria and ischemic lesions. Considering this symptomology and the gender of the patient, the clinician suspected FD and he performed the following analyses: ecocolordoppler TSA, eyes examination, cardiac examination, Rmi (*Figure 1*), urinary tract, radiography, and evaluation of specific symptoms with Mainz Severity Score Index.
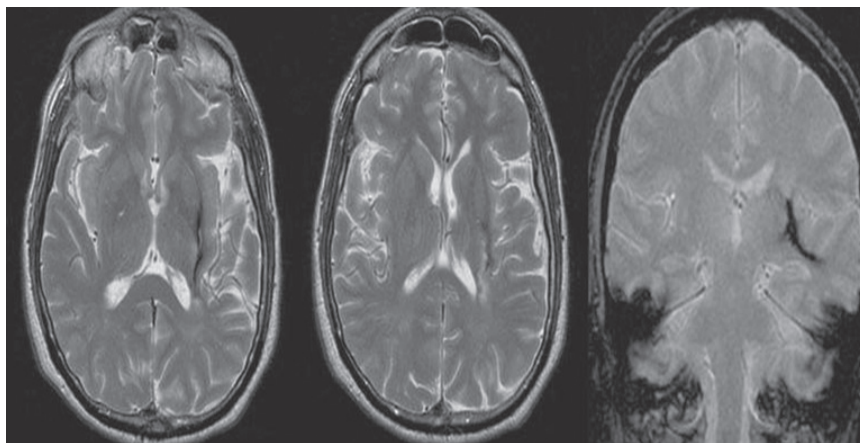
Figure 1.

In order to confirm the clinical suspect of FD, the genetic test for FD was performed in this patient: peripheral blood of the patient was collected, using EDTA as an anticoagulant. The DNA sample was isolated from whole blood using GenElute™ Blood Genomic DNA Kit (Sigma-Aldrich, St. Louis, MO, USA). The exons of the GLA gene, the intronic regions flanking them, and the IVS4 were amplified. Purified PCR products were sequenced using the automated DNA sequencer. This analysis revealed the mutation p.S126G, an alteration that was already described in patients with cerebrovascular symptomatology (Brouns et al., 2010; De Brabander, 2013). However, the involvement of this alteration in FD is still controversial.

We extended the genetic analysis to other relatives and we found the same mutation in proband's mother, twin sisters and daughter (*Figure 2*).

Neuropsychological battery was administered to proband for the assessment of a possible cognitive impairment. In particular, we used a traditional "face to face" modality for administration of neuropsychological tests. Firstly, a psychological interview was performed before the beginning of the test, while in the second meeting was administered the neuropsychological battery. The neuropsychological battery was constructed in order to integrate tests that assess different cognitive domains. Specifically have been investigated: global cognitive efficiency, attention, memory, language, logical reasoning and spatial cognition.

The global cognitive efficiency has been investigated through the Mini Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975).
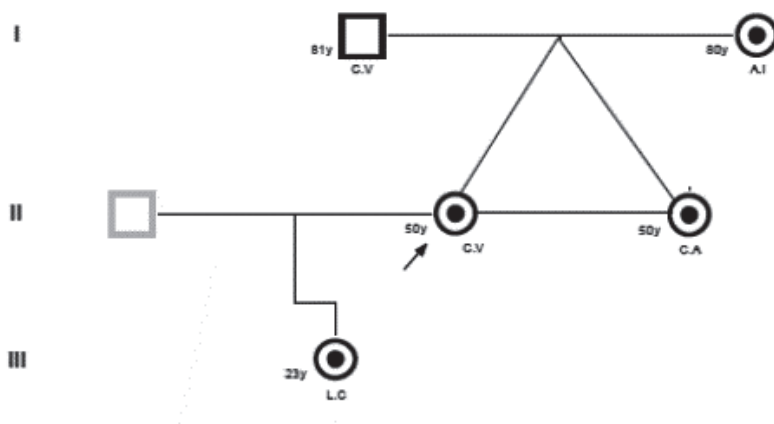

Figure 2.

The attention has been investigated through the Trail Making Test (TMT A and B) (Reitan, 1958; Giovagnoli et al., 1996), the Paced Auditory Serial Addition Task (PASAT) (Gronwall, 1977) and the Stroop Color Word Interference Test (Golden, 1978; Venturini, Lombardo Radice & Imperiali, 1983).

The TMT A and B evaluate the attentional skills, cognitive flexibility, the shifting abilities and spatial planning in a visual-motor task type. The PASAT test examines the auditory-verbal divided attention involving selective and sustained attention and the STROOP test is a test for the assessment of visual attention (Caffarra, Vezzadini, Dieci, Zonato & Venneri, 2002).

The short-term memory has been investigated through the test Digit Span (verbal memory span) (Wechsler, 1945; 1955; 1981; 1987; Orsini et al., 1987) and the Corsi Test (visual-spatial memory span) (De Renzi & Nichelli, 1975; Orsini, 1987; Spinnler & Tognoni, 1987).

Thelong-term verbal memory was investigated with the Rey Auditory Verbal Learning Test (AVLT) (Taylor, 1959; Rey, 1964; Carlesimo et al., 1995) which measures the span of immediate memory and provides an assessment on learning, while the long-term visuospatial memory was investigated with the Corsi Supra Span (Spinnler & Tognoni, 1987) and the Rey Complex Figure Test (RCFT) (Caffarra, 2002; Carlesimo et al., 2002).

Through the Modified Wisconsin Card Sorting Test (MWCST) (Berg, 1948; Grant & Berg, 1948) we have evaluated abstract reasoning skills and change of cognitive strategies to changing environmental circumstances; with Frontal Assesment Battery (FAB) executive functions were investigated (Appollonio et al., 2005).

The language has been investigated with phonological (FAS; Carlesimo, 1995) and semantics (Fruits + Animals + Colours) fluency (Novelli et al., 1986).

Finally, spatial cognition has been investigated through the copy of the Rey Complex Figure Test (RCFT).

It was also evaluated the level of quality of life and the presence of depressive symptoms through the use of Questionnaire SF36 and Hamilton Rating Scale for Depression (HDR-S). The SF36 is a questionnaire that explores the patient's health condition, it is characterized by brevity and precision. It is a multi-dimensional questionnaire articulated through 36 questions divided into 8 different scales. The 36 questions are conceptually related to 8 health domains: AF – physical activity, RP – role limitations due to physical health and RE – role limitations due to emotional problems, BP – physical pain, GH – perception of general health, VT – vitality, SF – social activities, MH – mental health and a single question on change in health status. The SF36 questionnaire can be self-administered, or may be presented throw a telephone interview or face-to-face. The HDR-S is a scale that explores 21 different areas that are crucial for the evaluation of the depressive state of the subject.

Table 1.

Test	Corrected score	Cut-off
MMSE	27.94	≥ 23.8
Verbal memory		
Digit Span	3.75	≥ 3.75
RAVLT - immediate recall - delayed recall	 31.5 4	 ≥ 28.53 ≥ 4.69
Visual-spazial memory		
(RCFT) - immediate recall - delayed recall	 13.24 12.09	 ≥ 6.33 ≥ 6.44
Span Corsi	5.75	≥ 3.5
Supra Span Corsi	10.44	≥ 5.5
Stroop Color Word Interference Test (short)		
- read words (W) sec.	14	≤ 38
- color designation (C) sec.	19	≤ 35
- interference (CW) sec.	40	≤ 80
- time interference effect	25.5	≤ 36.91
- interference effect errors	0	≤ 4.23
Trail Making Test		
Test A sec.	41	≤ 93
Test B sec.	143	≤ 282
MWCST - categories	3	≤ 3
MWCST - errors	8	
Perseverative errors	14	≤ 6.4
Percentage perseverations	100%	
FAB – Frontal Assess Battery	17.7	≥ 6.33
PASAT 3	21.9	≥ 28.4
PASAT 2	16.33	≥ 17.1
Verbal fluency		
F + A + S	25.3	≥ 17.35
Fruits + Animals + Colours	42	≥ 25
Constructional praxis		
RCFT – Copy	36	≥ 28.88
Hamilton Rating Scale for Depression	2	< 7
SF36	6	
Mainz Severity Score	14	slight

The areas are: depressed mood, guilt, suicide ideas, initial insomnia, middle insomnia, prolonged insomnia, work and interests, slowing of thought and words, agitation, anxiety of psychic origin, anxiety of somatic origin, gastro-intestinal somatic symptoms, general somatic symptoms, genital symptoms, hypochondriasis, introspection, weight loss, diurnal variation of symptoms, depersonalization, paranoid symptoms, obsessive symptoms. Each of the 21 areas is an individual scale, which is given a score ranging from 1 (absent) to 5 (severe), or 1 (absent) to 3 (clearly present), depending on the items and the severity of symptoms. Subsequently, the examiner will give a total value for each area surveyed, using a score of 0 (absent), 1 (mild), 2 (moderate), 3 (severe), or 4 (very severe) points. The total score is calculated by summing the points (0 to 4), of each of the 21 areas investigated. The rating obtained is indicative of a possible depression if it is comprised between 10 and 15 points, of a mild depression if it is comprised between 16 and 25 points, of moderate depression if it is between 26 and 28 points, and in case severe depression it is greater than 28 points.

The correction of neuropsychological test showed that the global cognitive efficiency was not pathological, but some specific functions were not normal (*Table 1*). The patient presented results below the cut-off to test Pased Auditory Serial Addiction Task (PASAT) showing a sustained and divided attention deficit, the Rey Auditory Verbal Learning Test (RAVLT) showing deficit in delayed recall test and at the Modified Wisconsin Card Shorting Test (MWCST) perseveration were found. The memory disorder was also reported by the patient, since he said he has suffered from decline in cognitive performance in recent years.

As regards the tests that investigate the level of quality of life and the presence of depressive symptoms no alterations were revealed.

3. Discussion

There are several studies that have investigated the neurological manifestations and possible cognitive impairment in individuals with FD, or in individuals with symptoms referable to FD and with a controversial mutations in the GLA gene. Our work is aimed at the study of this aspect. Furthermore, there are cases of patients with cerebrovascular suffering in the absence of other significant signs of disease. In the FD, the existence of cerebrovascular damage could be considered the critical variable in terms of cognitive performance. However, in a study of a sample of individuals with first lacunar stroke (common in FD), this was not associated with an increased

risk of cognitive impairment within a year from the event (Anderson et al., 2008). Against the assumption, Fabry patients with marked brain structural alterations, showed only mild cognitive deficits and the high frequency of depression in FD is likely to be related to the burden of this chronic disease, but not to the FD-typical brain structural alterations (Schermuly et al., 2011).

The patient showed a mutation in the GLA gene, p.S126G, which is an alteration with a controversial role in the onset of pathology. In fact, it was already described in patients with stroke but no other signs or symptoms referable to FD (Anderson et al., 2008; Sims et al., 2009). In our study, the patient presented also other clinical manifestations of FD, like acroparesthesias, TIA, mild tinnitus, fatigue, proteinuria and ischaemic lesions. However, it is not possible to associate this mutation to FD phenotype. Other molecular studies are necessary in order to clarify the involvement of p.S126G in the pathogenetics of the disease. However, the cognitive profile of the patient studied (in relation to the presence of specific deficits of sustained and divided attention and of executive function in the absence of a general cognitive impairment) appears to be similar to those of patients FD. The patient, in fact, has no marked cognitive disorders confirming what is described in the literature (Segal et al., 2010; Elstein et al., 2012) while expressing subnormal performance in some tests. In particular, the patient experiences a general cognitive difficulties appeared in recent years, characterized by a slowdown in processing information skills, as sustained attention deficit and long-term verbal memory disorders. In our case, with mutation p.S126G, cognitive impairment seems not determined by depressive symptoms that do not appear significant. The case requires a reassessment to monitor possible cognitive impairment. As well as, in line with the literature, it repents the need for an extension of neuropsychological assessments in all the patients with FD in sample loading at our center.

Through the study of neuroimaging and clinical and cognitive status of patients with FD, it will be possible to clarify the type of relationship between cognitive impairment, the disease and its variants.

4. Conclusions

In this clinical case, we reported the neuropsychological profile of a patient with a controversial mutation in the GLA gene. The cognitive assessment showed a normal global cognitive efficiency and a selective impairment of the executive functions and of the ability to recall the verbally learned infor-

mation. Scores below the average were recorded in a sustained and divided attention, in the cognitive flexibility and in the presence of perseveration. This neuropsychological profile is similar to the profile reported in other studies. Some studies, in fact, show a mild cognitive impairment and decline primarily attributable to the attentional and executive function skills. However, the work on the assessment of cognitive impairment has several limitations. It is not yet possible to establish a clear correlation between cognitive impairment, cerebrovascular symptoms and possible causes other consequential to the disease and its variants. Longitudinal studies are needed to explain, if the mild cognitive deficits in FD could precede a significant cognitive decline.

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