

Cognitive Testing in Fabry Disease: Pilot Using a Brief Computerized Assessment Tool

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ABSTRACT: **Background:** Recently, cognitive assessments of patients with Fabry disease highlighted neurocognitive impairment using test batteries that are time and labor intensive.

Objectives: To introduce a user-friendly self-administered tool for cognitive testing in patients with Fabry disease.

Methods: We used a computerized system requiring about 1 hour for patient follow-up. All patients with enzymatic and/or molecular diagnosis of Fabry disease seen in our clinic underwent assessment with the Fabry-specific Mainz Severity Score Index (MSSI) with subscores (neurological, renal, cardiac, and general) and a Mindstreams neurocognitive battery for mild impairment, evaluating memory, executive function, attention, information processing, visual spatial processing, verbal function, and motor skills. A Global Cognitive Score (GCS) was also computed.

Results: Ten patients (3 males, 7 females) were tested (mean age 41.5, range 25–56 years). Males were younger, had moderate nephropathy and no cerebrovascular accident (CVA); their Mindstreams GCS was 85.6–107 points. Three females had mild-moderate (8,10,15 points) neurological MSSI subscores (two CVA); all females had Mindstreams GCS of 59–107.7 points. Below-average performance was prevalent, particularly in information processing and motor skills consistent with mild impairment. Average GCS in females (90.3 points) was lower than in males (98.2 points). For individual patients, performance was poorest in information processing (n=4), attention (n=2), motor skills (n=2), verbal function (n=1), and visual spatial processing (n=1).

Conclusions: MindStreams may simplify cognitive assessment monitoring in Fabry disease.

IMAJ 2012; 14: 624-628

KEY WORDS: Fabry disease, MindStreams, NeuroTrax, cognitive testing, Mainz Severity Score Index (MSSI), cerebrovascular events

females [1]. Since the genetics of Fabry disease follow X-linked inheritance (the gene is found at position Xq22.1) predictions [2], and in view of the Lyon hypothesis of inactivation of one X-chromosome [3], hemizygous males evince classic signs and symptoms of Fabry disease whereas in females the clinical picture reflects the number of inactivated chromosomes.

Storage, and hence pathological disease, occurs preferentially in renal glomerular and tubular epithelial cells, myocardial cells, heart valve fibrocytes, neurons of dorsal root ganglia, and endothelial smooth muscle cells of blood vessels. The more prominent symptoms, most of which are progressive with age, are pain crises and acroparesthesia, angiokeratoma, renal dysfunction, cardiac left ventricular hypertrophy, hypohidrosis and anhidrosis, and cerebrovascular dysfunction and cerebral ischemia [4]. Psychiatric symptoms, particularly depression, pain attacks, poor psychosocial adjustment, and impaired quality of life from childhood, are recurrent and pervasive complaints [5]. The course of untreated illness is unremitting, albeit with variability in terms of onset and severity, and there is significant mortality particularly in patients with early-onset stroke [6].

Since 2001, two enzyme replacement therapy options that putatively halt the disease progression considerably and alleviate many symptoms have become available [7,8]. Nonetheless, among the signs that may be less amenable to improvement with the current ERT modality are the neuropsychological/psychiatric features [5] since they are apparently a result of sphingolipid deposits in the endothelium of small cerebral vessels that lead to regional cerebral ischemia, which is irreversible [9].

Recently, a psychiatric and cognitive profile of Israeli patients with Fabry disease [10] highlighted several features that imply neurocognitive involvement but which cannot be attributed solely to the existence of a chronic disease with significant chronic pain (and which do not seem to resolve despite years of ERT), and depression [11]. The findings by Segal et al. [10] included generally normal performance on most cognitive measures, although the speed of information processing and some executive functions were subnormal. These researchers recommended the use of neurocognitive assessment for patients with Fabry disease. The battery of tests that were used by Segal et al. [10] included a Wechsler Intelligence Scale (for

ERT = enzyme replacement therapy

Fabry disease is an inborn error of metabolism where deficiency of the lysosomal enzyme α -galactosidase A results in progressive systemic deposition of glycosphingolipids, predominantly globotriaosylceramide, in affected males and

adults or children as required), the Rey-Osterrieth Complex Figure Test and delayed reproduction of the Rey-Osterrieth Complex Figure Test, the Kave Naming Test, choice reaction time tests and motor tapping, the Rey Auditory-Verbal Learning Test, digit span forwards and span of visual memory test, Integneuro CPT test, the Trail-making Test, the first part of the Stroop Test, the digit symbol subtest of the Wechsler Intelligence Scale (for adults or children as required), and a psychiatric set including a semi-structured interview using the SADS/K-SADS questionnaire (for adults or children as required). These tests were different from those employed by Low and co-workers [12] and indeed resulted in detection of milder features. The conclusions of Low et al. [12] were that serious neurological complications were present in all evaluated patients but that cognitive testing was basically normal.

Mindstreams® (NeuroTrax Corp., NY, USA) was designed to provide a comprehensive assessment with the added advantages of greater objectivity, shorter testing time, and precise response time measurement. The Mindstreams tool, although well-characterized and validated, with good test-retest validity [13], was not designed to substitute for the full complement of batteries employed by psychologists and psychiatrists which may be necessary for more complicated neurological and/or psychiatric signs. Nonetheless, if the intent is to track cognitive performance over time and/or in the presence of therapeutic interventions, a self-administered test that is easy to administer [14] and provides automatic and immediate scoring and reporting may be justified. Moreover, the mainstay of Mindstreams is its ability to assess mild impairment [15].

Our group regularly monitors a small cohort of patients with Fabry disease, most of whom receive ERT. It was our intention to incorporate neurocognitive testing but we chose Mindstreams, a less time-consuming computerized system that was both user-friendly and with which the patients are compliant at regular intervals. This is in line with recommendations to progress towards more evidence-based and computerized assessment tools [16].

We report our findings in 10 adult Israeli patients with Fabry disease using a standardized tool for neurocognitive testing, which we believe supplies much of the clinically relevant information. It was the objective of this pilot study to ascertain whether the results were comparable to those of other groups using more time- and labor-intensive systems.

PATIENTS AND METHODS

All adult patients with enzymatic and/or molecular diagnosis of Fabry disease seen in our clinic were included. All underwent standard intake evaluations and were also assessed by the Fabry-specific MSSI (Mainz Severity Score Index) [17]. This scoring system awards points on the basis of increased severity for each of four categories: general, neurological, cardiac, and

kidney involvement. The combined “total” score of subscores can then be used to compare severity over time in the same patient and also between patients or groups of patients. For each category 1–10 points is considered mild disease, 11–20 points is considered moderate, and > 21 points severe.

A Mindstreams computerized cognitive battery for mild impairment [15] was administered to all patients as part of the intake evaluation. Mindstreams analyzes outcome parameters computed across single trials: namely, stimulus onset and offset (in milliseconds), expected response, actual response, and time of response. Performance in study individuals is automatically standardized relative to cognitively healthy individuals of similar age and years of education drawn from a database of individuals participating in controlled research studies (with no cognitive, neurological, or psychiatric complaints or signs on medical evaluation). To permit averaging performance across different types of outcome parameters (e.g., accuracy, response time), normalized (standardized) scores are fit to an IQ-style scale (average = 100, SD = 15). Standardized outcome parameters that measure similar cognitive functions were averaged to produce seven ‘index scores’, each summarizing performance in a single cognitive domain [15]. The following index scores are computed: memory, executive function, attention, information processing speed, visual spatial processing, verbal function, and motor skills. Global Cognitive Score reflecting general cognitive status is computed as the average of the index scores.

Both disease-specific clinical severity scoring (MSSI) and the cognitive assessment (Mindstreams) are part of the routine follow-up evaluations for patients in the Fabry Clinic at our institution. Therefore, no institutional review board approval was needed for this study. We have used this system, a disease-specific severity scoring in conjunction with the Mindstreams evaluation, to assess patients with other lysosomal diseases in our institution and have shown that the results compare favorably with those of a traditional full-scale battery [18,19].

RESULTS

There were 10 patients: 3 males (25, 35 and 35 years old at the time of testing) and 7 females (aged 36–56 years at the time of testing). MSSI subscores and total MSSI score as well as GCS on the Mindstreams battery are presented for each patient in Table 1. This allows comparison of the neurological component of the MSSI versus the neurocognitive (Mindstreams) performance of each patient. Genotyping was not included in the table to preserve the anonymity of the patients since each (other than a sibling set, one male and one female) has a unique genotype.

All but three of the females (whose performance on the GCS was in the normal range, > 100 points) were concerned about

MSSI = Mainz Severity Score Index

tests of ‘intelligence’ and spontaneously volunteered to some degree their histories of poor academic and social adjustment.

Only descriptive statistics were used because of the very small cohort, albeit in what is recognized as an orphan disease

especially in Israel where fewer than 30 patients with Fabry disease to date have been identified.

Regarding the subscores of the MSSSI, three of the females had findings of mild to moderate (8, 10, and 15 points) neurological involvement (two with history of cerebrovascular events); the most affected was the oldest patient in the group. Only two of the three males had points in the MSSSI subscore for neurological involvement, and these were for depression and/or vertigo (1 or 2 points). All three males had moderate (12 points) renal disease (tubular disease and proteinuria), whereas only one female had renal involvement (tubular disease and proteinuria, 12 points). No correlation can be seen when comparing the GCS scores with the total MSSSI scores [Figure 1].

Table 1. MSSSI scores in patients with Fabry disease

Gender	Age at testing	MSSSI	MSSSI subscores				Mindstreams	
		Total	Neurologic	Renal	Cardiac	General	GCS	Score ≥ 1 SD
1 M	25	12	0	12	0	0	107	None
2 M	35	18	2	12	0	4	85.6	Attention
3 M	35	18	1	12	0	5	102.1	Visual spatial
4 F	48	8	2	0	0	6	97.3	Information processing
5 F	53	14	0	0	14	0	95.6	None
6 F	36	5	0	0	2	3	107.7	None
7 F	56	15	15	0	0	0	59	All
8 F	41	10	8	0	0	2	102.2	None
9 F	43	13	10	0	0	3	100.1	None
10 F	43	12	0	12	0	0	70.4	All

The scores reflect the severity of Fabry disease, and scores ≥ 1 standard deviation (SD) below normal (normalized, i.e., standardized) scores are fit to an IQ-style scale (average = 100, SD = 15) for healthy populations; hence ≥ 1 SD is outside the normal range on the Mindstreams measures (see text) in each patient.
GCS = Global Cognitive Score (the composite score, see text)

Table 2. Scores for each index category

	1 M	2 M	3 M	4 F	5 F	6 F	7 F	8 F	9 F	10 F	Mean
Memory	97.5	93	105.8	100.7	105.3	107.8	61.2	101.9	108.5	67.3	93.2
Executive function	109.2	88.3	115.5	107.5	92.1	112.6	53	102.1	109.2	74.5	93
Attention	112.4	70	108.7	97	93.1	107.6	26.7	101.5	103.3	83.1	87.5
Information processing speed	101.5	75	122.5	82.3	89.3	94.9		93.5	88.8	79.9	88.1
Visual spatial	122	83.9	74.3	85.6	94.8	114.2	76.1	109.5	96.5	69.3	92.3
Verbal function	111.4	91.3	82.7	110.4	102.8	109.3	78.1	107.3	105.6	38.2	93.1
Motor skills	94.7	97.6	105	97.5	91.9	107.7		99.6	88.5	80.7	94.3
Global Cognitive Score	107	85.6	102.1	97.3	95.6	107.7	59	102.2	100.1	70.4	90.3

See Methods section for full description of the Mindstreams neurocognitive test measures for each individual patient and the mean score for the group for each of these index categories, allowing comparison of performance intra-patients and inter-patient as well as a composite of the group performance in each index category

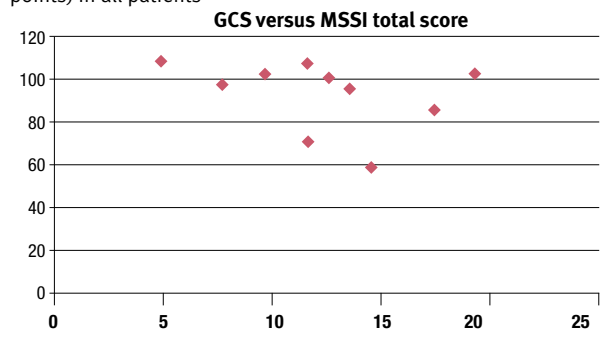
Table 2 presents the Mindstreams results for all patients. There were three patients, one male and two females, whose results were all below average (including those with insufficient responses to compute a score), two of whom scored more than one standard deviation (SD, 15 points) below average. One of these (#7, female) had serious neurological involvement and scored 15 points on the MSSSI neurological subscore, possibly related to a prior stroke. Of the remaining patients, all had 1–5 domain index scores below average.

Information processing speed and motor skills scores were below average in eight patients (including those who gave insufficient responses to compute a score in these domains). Many scores were below average but not more than one SD below average, a range consistent with mild impairment. Indeed the mean score across patients was in this range for all domains and the GCS [Table 2].

The mean GCS performance of the females (90.3) was lower than that of the males (98.2) as were each of the mean subscores, but this was not statistically significant (post-hoc *t*-test).

The domains in which individual patients performed poorly were processing speed (n=4), motor skills (n=2), attention (n=2), visual spatial function (n=1), and verbal function (n=1).

Figure 1. Graph comparing Global Cognitive Score on Mindstreams (0–120 points) versus the total Fabry disease MSSSI score (0–25 points) in all patients



DISCUSSION

Using a brief computer-administered commercially available neuropsychological test battery we were able to detect impairments in this cohort, where previously a very extensive hours-long battery was needed [10]. Moreover, we confirm that the pattern of impairment among these patients was mild but not specifically confined to any one domain. This latter finding is unlike our findings in (Israeli) patients with Gaucher disease [18], where visual spatial function was uniquely affected, and in (Israeli) patients with late-onset Tay-Sachs disease [19], where verbal function and executive function were most significantly affected. Based on these three studies using the same Mindstream tool in patients with three different lysosomal storage disorders, one can see a possible hint of differential disease-specific patterns in cognitive functioning. A further

hypothesis to consider is that abnormal storage material in the brain of the different lysosomal disorders may be disease specific and not have a common target or reservoir in the brain/central nervous system [20].

Alternatively, in the case of Fabry disease, the existence of cerebrovascular damage and stroke might be the critical variable in impaired cognitive performance. However, in a study of non-aphasic individuals who had a first-ever lacunar stroke (common in Fabry disease), this was not associated with an increased risk of cognitive impairment within a year of the event [21]. Similarly, and again counter-intuitively, in a study of relatively young patients with Fabry disease [13] including those with marked structural brain lesions/alterations, only mild cognitive deficits were noted. In this latter study of German patients with Fabry disease, only deficits in attention were found. Others have reported clinically significant abnormal cerebellar tests in the absence of symptomatic cerebrovascular disease among patients with Fabry disease [12], but here too, neurocognitive function was relatively normal. In addition, it was shown that depression was not correlated with the typical Fabry brain structural alterations, suggesting [13] that depression in Fabry disease, which is a (realistic) reaction to the multi-organ nature of the disease, may be the reason for poor cognitive performance (i.e., attention) rather than a consequence of neurological impairment. Our findings suggest that processing speed and motor skills are impaired, each of which is a distinct function but both are related to deficits in attention.

Females in the present study performed less well in all domains than did the males. There is no doubt that the very small number of seven females when compared to only three males, all younger than the females, is a critical limitation of the study. Nonetheless, since females have apparently higher rates of neurological involvement [22], the implication may be that they are at greater risk of cognitive impairment. It might be noteworthy that the poor cognitive performance in the females was not only associated with a high MSSSI neurological subscore.

In conclusion, we suggest that there is a pattern of cognitive impairment in Fabry disease, although it is relatively mild in adult patients who have not suffered cerebrovascular damage. The most affected domains appear to be speed in information processing and motor skills. Females may have some degree of neurocognitive impairment not necessarily associated with cerebrovascular events. The affected domains in Fabry disease are dissimilar to those seen in patients with other lysosomal diseases. These findings are comparable to those reported by others in patients with Fabry disease but we employed a system that can be used for long-term follow-up. The Mindstreams system is not time or labor intensive and patients do not find it objectionable because it generally can be completed within an hour. Finally, despite the small cohort, cognitive function using this user-friendly but comprehensive computer-based system and, importantly, in conjunction with

a disease-specific severity score (MSSI) may be appropriate, easier to perform, and clinically relevant as a marker of the natural cognitive course in Fabry disease. We believe this measure may warrant consideration as an outcome measure for future therapeutic interventions that impact on neurological processes in Fabry disease as well as other lysosomal disorders.

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Capsule

New mutations in melanoma

Despite the increased use of sunscreens, the incidence of melanoma, the most lethal form of skin cancer, remains high. Tumor genome sequencing has led to new therapies targeting BRAF, a protein kinase that is activated by mutation in about 50% of melanomas and helps drive tumor growth. Because the development of resistance to BRAF inhibitors limits their long-term efficacy, there is considerable interest in identifying additional driver mutations that might form the basis of new or combination therapies. Toward this end, Krauthammer et al. (*Nat Genet* 2012 10.1038/ng2359) sequenced the protein-coding regions of 147 human melanoma genomes. Notably, 9% of sun-

exposed melanomas harbored a point mutation in RAC1, which encodes a small GTPase (an enzyme hydrolyzing guanosine triphosphate) that regulates cytoskeletal rearrangements. Structural and functional analysis revealed that the mutation increases RAC1 binding to its downstream effectors, including PAK1 (p21-activated protein kinase), and induces melanocyte growth and migration. PAK kinases are therefore potentially druggable targets for melanoma treatment. In independent work, Hodis et al. (*Cell* 2012; 150: 251) found the same activating RAC1 mutation in 5% of their melanoma samples.

Eitan Israeli

Capsule

TNF receptor 1 genetic risk mirrors outcome of anti-TNF therapy in multiple sclerosis

Although there has been much success in identifying genetic variants associated with common diseases using genome-wide association studies (GWAS), it has been difficult to demonstrate which variants are causal and what role they have in disease. Moreover, the modest contribution that these variants make to disease risk has raised questions regarding their medical relevance. Gregory et al. investigated a single nucleotide polymorphism (SNP) in the *TNFRSF1A* gene, that encodes tumor necrosis factor receptor 1 (TNFR1), which was discovered through GWAS to be associated with multiple sclerosis (MS) but not with other autoimmune conditions such as rheumatoid arthritis, psoriasis and Crohn's disease. Analysis of the MS GWAS data in conjunction with the 1000 Genomes Project data provides genetic evidence that strongly implicates this SNP, rs1800693, as the causal variant in the *TNFRSF1A* region. The

authors further substantiate this through functional studies showing that the MS risk allele directs expression of a novel, soluble form of TNFR1 that can block TNF. Importantly, TNF-blocking drugs can promote onset or exacerbation of MS, but they have proven highly efficacious in the treatment of autoimmune diseases for which there is no association with rs1800693. This indicates that the clinical experience with these drugs parallels the disease association of rs1800693, and that the MS-associated TNFR1 variant mimics the effect of TNF-blocking drugs. Hence, their study demonstrates that clinical practice can be informed by comparing GWAS across common autoimmune diseases and by investigating the functional consequences of the disease-associated genetic variation.

Nature 2012; 488: 508

Eitan Israeli

A doctor has opportunities for studying human nature which are given to no one else, wherefore a philosopher ought to begin his life as a doctor, and a doctor should end his life by becoming a philosopher

Ancient Greek saying