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Psychiatric and Cognitive Characteristics of Individuals with Danon Disease (*LAMP2* Gene Mutation)

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Abstract

Danon disease (DD) is a rare X-linked disorder caused by loss-of-function mutations in the *LAMP2* gene, which encodes lysosome-associated membrane protein. It is characterized by the triad of hypertrophic cardiomyopathy, myopathy, and intellectual disability. Whereas the molecular and pathophysiological mechanisms underlying this disorder have been previously reported and continue to be explored, the cognitive deficits and psychiatric comorbidities manifested in DD remain an understudied topic. We systematically assessed cognitive abilities and psychiatric comorbidities in 13 males and females. Most of the participants in our cohort (n=9; 75%) had an IQ score within the normal range, while only one participant had intellectual disability. Participants' performance on the Cognitive Neuropsychiatric Battery (CNB) showed only mildly impaired cognitive abilities in most modules, except in the executive functioning test, which was low compared to healthy controls. Of note, 69% of the participants met criteria for at

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least one psychiatric disorder, mainly mood and anxiety disorders, occurring alone or in combination in the same patient. The results of the present study challenge earlier reports suggesting that mental retardation is a core constituent in DD. Of importance, it underscores the need to refer Danon patients to psychiatric assessment.

Keywords

Danon disease; IQ; cognition; psychiatric comorbidities; *LAMP2*; Cardiomyopathy; Wolff-Parkinson-White syndrome

Introduction

Danon disease (DD) is an X-linked metabolic disorder, also referred to as lysosomal glycogen storage disease (type IIb or Pompe with normal acid maltase; Danon et al., 1981). It was originally described by Danon et al. (1981) in two unrelated cases of 16 years old boys with triad of symptoms: cardiomyopathy, skeletal myopathy and intellectual disability. Most of the mutations associated with the disorder lead to a null allele resulting in absence or severe depletion of *LAMP2* protein expression (Nishino et al., 2000). Males usually develop the condition earlier than females and show a severe, rapidly progressive disease trajectory. Consequently, affected men live on average to the age of 19 years, while affected women live to an average age of 34.6 (Boucek et al., 2011).

Whereas the clinical phenotypes of the disorder are relatively well-known (Nishino et al., 2000; Maron et al., 2009), the cognitive deficits and psychiatric comorbidities manifesting in DD remain an understudied topic that merits further investigation. While the current literature suggests that most men and a fraction of affected women have intellectual disability (Sugie et al., 2002, 2016), to the best of our knowledge, cognitive abilities were not rigorously assessed in previous studies (Danon et al., 1981; Boucek et al., 2011). Same goes with reports on psychiatric comorbidities in DD which are almost entirely missing from DD medical literature (Hatz et al., 2010; Tanidir et al., 2015). In one study, formal IQ tests were performed in five male patients and their IQ was found to be in a range of 60-91 (Sugie et al. 2002).

Of note, the term “mental retardation” was originally used to describe the cognitive complaints in affected individuals, but since the publication of DSM-5 (American Psychiatric Association, 2013) the term was replaced to “intellectual disability” which we will use hereafter in the manuscript.

The purpose of the current study was to thoroughly characterize the cognitive and psychiatric profiles of individuals diagnosed with DD.

Materials and Methods

Participants

Thirteen participants (5 males and 8 females) with genetically confirmed *LAMP2* mutations were enrolled to the study. The patients originated from five medical centers at three

different countries: Israel (n = 8), Spain (n = 4), and Italy (n = 1) (see Table I for participants' socio-demographic characteristics). The Israeli cohort included all known living DD individuals currently residing in Israel, all being Ashkenazi Jews who carry the same founder mutation. The study was approved by the Institutional Review Boards (IRB) of the participating sites. An informed consent was obtained from participants and from parents of minors.

Cognitive Assessment

Full-scale IQ scores (FSIQ) of twelve participants were calculated using the age-appropriate version of the Wechsler Intelligence test (Wechsler, 1997). In addition, 7 Israeli participants underwent comprehensive neurocognitive assessment using the Penn Computerized Neurocognitive Battery (CNB) (Gur et al., 2010). The CNB is a single computerized battery which rules out potential limitations of combining tests from multiple batteries, and it is suggested to correlate with IQ (Swagerman et al., 2016). The CNB is widely employed in individuals with genetic syndromes (Weinberger et al., 2016).

The CNB includes 14 computerized tests assessing five neurocognitive domains (Executive Function, Episodic Memory, Complex Cognition, Social Cognition, and Praxis Speed). Each test yields an accuracy score (number of correct responses) and a speed score (median time for correct responses). For consistency of interpretation, higher positive scores were manipulated to reflect better task performance: response time scores were multiplied by -1, so that slower response time is reflected in lower scores and vice versa. Scores lower than -4 were set to a floor value of -4 to reduce the influence of outliers. Finally, efficiency scores were calculated by taking the arithmetic mean of the accuracy and speed scores. Global neurocognitive performance (GNP) score was calculated as the mean of all efficiency scores of the different modules of the battery.

Psychiatric Assessment

All participants underwent psychiatric assessment. The Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime (K-SADS-PL) was used to assess psychopathology in children and adolescents up to age 18 (Kaufman et al., 1997), and the Structured Clinical Interview (SCID) was used in case of adults (First et al., 1997).

Results

Medical and Genetic Characteristics

The present cohort included 13 patients, 5 males and 8 females. At the time of the study the age of the participants ranged from 17 to 57 years (mean age = 36.23 y, SD = 16.06). Participants had cardiological manifestations including Wolff-Parkinson-White (WPW), hypertrophic or dilated cardiomyopathy and congestive heart failure to various extents (table II). Of note, patients #1 and #3 were referred to the metabolic clinic for evaluation of hypertransaminasemia for evaluation of failure to thrive at age 6 months and prior to starting Ritalin (methylphenidate) due to ADHD at age 6 years, respectively. Their molecular diagnosis was established at age 10 and 8 years, respectively, while having no cardiological symptoms. No ophthalmological abnormalities were reported in this cohort. Three females

(#2, #4 and #6) did not manifest any of the classical features of Danon disease and were therefore designated as carriers. Patients #1-8, originating from the same Israeli kindred had the same splice site mutation. The other five participants had stop codon mutations.

Cognitive Characteristics

The mean FSIQ score of the entire sample was 89.0 ± 12.4 points. The mean FSIQ score of males (86.4 ± 17.5) did not differ from that of females (90.9 ± 8.3), $t_{(10)} = -.60$, $p = .62$. The lack of sex difference in FSIQ score repeated also when non-affected (carrier) females were excluded from the analysis, $p = .36$ (the mean FSIQ score of the 5 affected females was 94.4 ± 2.7). Of the 12 participants that completed FSIQ assessment, 9 individuals (75%) had a score greater than 90, within the normal range of intelligence (ranging between 91 and 105 points). Two participants had borderline intelligence (see patients #3 and #6 in Table III), and only one patient had a score within the range of intellectual disability (patient #12).

On the CNB, the mean GNP score was -0.94 (an equivalent to a FSIQ score of 86) with SD of 0.95, with more pronounced deficit in the executive function domain (-1.72 ± 1.27), compared to all other domains (which ranged between -0.96 and -0.34 ; Figure 1). Sex differences in GNP or the 5 CNB modules did not emerge, all p 's $> .05$ (p values ranged between .88 for GNP and .054 for Complex Cognition).

Psychiatric Comorbidities

At the time of psychiatric evaluation, 9 participants (69.2%) met criteria for at least one psychiatric disorder (Table II). We observed high rates of mood disorders (found in 6 out of 13 participants, 46.15%), including: major depression disorder (MDD; $n = 3$), and dysthymia ($n = 3$). Similarly, 6 out of 13 individuals met criteria for an anxiety disorder (46.15%), including: general anxiety disorder (GAD; $n = 3$), social anxiety disorder (SAD; $n = 2$), panic disorder ($n = 1$), and specific phobia ($n = 1$). Two patients were diagnosed also with attention deficit/hyperactivity disorder (ADHD), alongside a diagnosis of either oppositional defiant disorder (ODD; patient #3) or dysthymia (patient #6). One patient who was diagnosed with SAD and specific phobia (#1) also met criteria for the diagnosis of obsessive-compulsive disorder (OCD).

Finally, 2 female carriers ("asymptomatic carriers") were found to have psychiatric comorbidities, including dysthymia, ADHD and GAD.

Detailed Clinical Reports

Patients #1 and #5 originated from the same Israeli kindred (detailed article in preparation). About 50 years ago the first grandparent of this kindred was described (Kariv et al., 1971). At age 26 y, he presented with hypertrophic cardiomyopathy and WPW arrhythmia. He underwent pacemaker implantation and died of heart failure at age of 44 y. Few decades later, two of his grandchildren died with the same phenotype at age 35 y. Patient #1 is his great-grandson.

Patient #1: A 18 years old male. He was diagnosed with Hypertransaminasemia (with normal CPK) at age 6 months during evaluation of failure to thrive. At age 4 y, liver

histology revealed glycogen storage disease of unknown etiology. At the age of 12 y, while still asymptomatic, his mother (patient #2) reported the death of her two brothers. They presented since age 18 y with hypertrophic cardiomyopathy, WPW and hyperkalemia. Both died around 35 y of age, one following heart transplantation and the other succumbed to a sudden arrhythmia. The combination of progressive cardiomyopathy and WPW in the uncles, combined with the glycogen storage found in the liver of pt#1 led to the finding of the *LAMP2* mutation in this patient. Reportedly he was a good student, graduating from high school with high grades. On cognitive evaluation, he received FSIQ score of 94 points, within the average range of the general population. In the psychiatric assessment, he reported having a significant difficulty in conversation with others and a tendency to avoid any social activities in and outside school meeting the DSM-5 criteria of SAD. He also met criteria for OCD and specific phobia. At the time of the assessment, he was treated with tablets of escitalopram 20 mg per day for his anxiety symptoms with partial improvement.

Patient#5: A 17 years old male diagnosed with DD at the age of 14. While undergoing clinical assessment, he was living with his parents and with his non-affected younger brother. His asymptomatic mother (patient #6) was found to be a carrier of the kindred's mutation. Of note, his grandmother suffered from cardiomyopathy with advanced AV block and died of heart failure at age of 69 y. At present, he manifests hypertrophic, cardiomyopathy, hypertransaminasemia and elevated serum CPK. His parents indicated that he was a talented student with high grades showing no signs of cognitive impairment. On cognitive testing his FSIQ was 105 points, with his verbal IQ significantly higher than his performance IQ (117 vs. 89 points, respectively). He was diagnosed with SAD and dysthymia, with some symptoms evident since the age of 3 y. Significant improvement was noted after treatment with cognitive-behavioral therapy and fluoxetine up to 40 mg.

Patient#10: A 49 years old female diagnosed with cardiomyopathy when she was 19 years old and with DD mutation at the age of 23 y. She underwent heart transplant at earlier age. At the time of clinical assessment, she was single, had no children, and was living with her parents. At present, she copes with congestive heart failure, WPW and fibromyalgia. On cognitive testing her FSIQ was 98 points, with no difference between verbal and performance domains, but with marked inattention that seemed to lower her overall cognitive testing scores. Patient#10 describes herself as a "nervous person" and had panic attacks since she can remember herself. She was diagnosed with panic disorder and agoraphobia when she was 10 years old. In the current psychiatric interview, she met criteria for dysthymia and panic disorder. At the time of assessment, she was receiving psychotherapy combined with trazodone and duloxetine.

Discussion

Our study is the first to systematically assess the cognitive and psychiatric characteristics of males and females diagnosed with DD. We found that most patients have an IQ score within the normal range and only one patient had intellectual disability. Cognitive testing further revealed a relative weakness of DD patients in the domain of executive function. These findings partially contrast earlier reports, including the original description of the disease by Dr. Danon, which referred to intellectual disability as one of the disease's triad of symptoms

(Danon et al., 1981; Boucek et al., 2011). However, only a few studies assessed IQ and cognitive abilities using formal psychometric tests, and the ones to do so were either confined to small sample size or holds standardized data only on part of the sample (Sugie et al., 2002, 2016).

An earlier investigation reported that mental retardation was observed in 14 affected males (70% of that sample) and 1 affected female (6% of the sample). However, IQ was formally assessed only in 5 out of 20 males (Sugie et al., 2002). Another study that reported the findings of 82 individuals with DD from 36 families reported that mild to moderate learning or cognitive disabilities existed in all males and approximately half of affected females (Boucek et al., 2011). However, this study was based on registry data, not on direct clinical/cognitive assessment. A recent case report of a 12 years old girl with DD (Sugie et al., 2016) indicated that she had a learning disability and an intellectual disability, and an IQ score of 78 points, within the borderline range of intelligence, with perceptual reasoning being higher than verbal comprehension.

As our analysis suggest that when the cognitive abilities of DD patients are assessed using standardized cognitive measurements, most of them are not shown to have intellectual disability/mental retardation but rather milder cognitive (e.g., executive functioning) deficits.

The second novel finding concerns the high rates of psychiatric comorbidities, especially anxiety disorders and mood disorders, found in our sample of 13 individuals. More than two-thirds (69.2%) of the participants met criteria for at least one psychiatric disorder, and approximately half of participants (53.8%) were diagnosed with two or more psychiatric comorbidities. In addition, comorbidities were as common in hemizygous males as in heterozygous females and, remarkably, were present even in female “carriers” considered so far to be asymptomatic.

Although patients with cardiomyopathy are known to have higher incidence of mood and anxiety disorders (Dickens et al., 2012), reports regarding psychiatric illness in DD are scarce. In fact, to date, there are only two single case-studies describing clinical/psychiatric symptoms in individuals with DD. One study described the case of a 19 years old male with ADHD who developed psychosis and suicidal ideations few years after undergoing a heart transplant (Hatz et al., 2010). The second case study described a 16 years old male with mood and anxiety symptoms (Tanidir et al., 2015). Our findings indicate that clinicians and caregivers dealing with DD patients should be aware of their proneness towards depressive and anxiety disorders.

Moreover, these psychiatric comorbidities may affect compliance with the medical treatment and activity recommendations given to DD patients due to their cardiac condition. Since effective regimens such as CBT and selective serotonin reuptake inhibitors (SSRIs) are readily available (Papakostas et al., 2008; Hofmann et al., 2012), timely psychiatric evaluation is warranted in all newly diagnosed subjects with *LAMP2* mutations, regardless of whether they show the typical DD medical (cardiac) symptoms or not.

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Figure 1. Computerized Neurocognitive Battery (CNB) Mean Standardized Score and Standard Deviations of the Israeli Sample

Table I

Sociodemographic Characteristics

Family	Patient	Age at Evaluation *	Sex	Country	Years of education	Independent living	Marital status	Number of Children (Affected)
1	# 1	18	Male	Israel	12	Lives with parents	Single	0
	# 2	46	Female	Israel	NA	Independent	Married	2 (1)
2	# 3	15	Male	Israel	10	Lives with parents	Single	0
	# 4	43	Female	Israel	12	Independent	Married	4 (2)
3	# 5	17	Male	Israel	12	Lives with parents	Single	0
	# 6	46	Female	Israel	12	Independent	Married	2 (1)
4	# 7	56	Female	Israel	9	Independent	Widow	5 (NA)
5	# 8	36	Male	Israel	12	Lives with parents	Single	0
	# 9	19	Female	Italy	12	Lives with parents	Single	0
7	# 10	49	Female	Spain	12	Lives with parents	Single	0
	# 11	49	Female	Spain	12	Independent	Married	2
9	# 12	20	Male	Spain	9	Lives with parents	Single	0
10	# 13	57	Female	Spain	9	Independent	Divorced	1

* Age at psychiatric and cognitive evaluation.

Table II

Clinical, Genetic, and Psychiatric Characteristics

Family	Patient/Sex	Age at clinical presentation (y)	Type of mutation	Medical comorbidities	Medications	Psychiatric comorbidities
1	# 1/M # 2/F	6 months Carrier	Splicing Splicing	ECG-WPW, Impaired LFT None	Escitalopram None	SAD, OCD, Specific phobia GAD
2	# 3/M # 4/F	4 Carrier	Splicing Splicing	Impaired LFT, CPK, 1 st AV block None	None None	ADHD, ODD None
3	# 5/M # 6/F	14 Carrier	Splicing Splicing	CMP, impaired LFT, CPK None	Fluoxetine Escitalopram	SAD, Dysthymia Dysthymia, ADHD
4	# 7/F	50	Splicing	HF, CMP, Arrhythmia	Amiodarone, Verapamil	GAD, Major depression
5	# 8/M	18	Splicing	CMP, Impaired LFT, CPK	Bisoprolol, Perphenazine, Clonazepam	GAD, Panic disorder, Major depression
6	# 9/F	14	Stop codon	Hypertrophy, ECG-WPW	Bisoprolol	None
7	# 10/F	23	Stop codon	HF, CMP, ECG-WPW	Trazodone, Duloxetine	Dysthymia, Panic disorder
8	# 11/F	32	Stop codon	HF, CMP, ECG-WPW	None	None
9	# 12/M	5	Stop codon	CMP, Impaired LFT, CPK, ECG-WPW, Myopathy	None	None
10	# 13/F	37	Stop codon	CMP, HF, impaired LFT, 1 st AV block	Fluoxetine, Lorazepam	Major depression

CMP, Cardiomyopathy; Impaired LFT, impaired liver function test; CPK, creatinine phosphokinase; ECG, WPW, Wolff-Parkinson-White; SAD, social anxiety disorder; OCD, obsessive compulsive disorder; GAD, generalized anxiety disorder; ADHD, attention deficit/hyperactivity disorder; Families 1-5 belong to the same Israeli kindred.

Table III

Cognitive Characteristics

Family	Patient	Wechsler version	FSIQ	Computerized Neurocognitive Battery (CNB)					
				EF	CC	SC	EM	PS	GNP
1	# 1/M	WAIS-III	94	-3.51	-0.84	-1.42	-0.26	-0.68	-1.34
	# 2/F	WAIS-III	91	-0.74	-0.24	0.02	0.25	-0.81	-0.30
2	# 3/M	WISC-R-95	75	-0.96	-1.51	-0.95	-1.02	-0.177	-0.93
	# 4/F	WAIS-III	NA						
3	# 5/M	WAIS-III	105	-1.10	-0.67	-0.87	-0.05	-0.69	-0.68
	# 6/F	WAIS-III	73	-1.94	-0.55	-0.67	0.22	-0.66	-0.72
4	# 7/F	WAIS-III	91	-3.40	NA	-1.70	-0.94	-0.68	-1.68
	# 8/M	WAIS-III	96	-0.41	-1.46	-1.08	-0.58	-0.94	-0.89
6	# 9/F	WAIS-IV	96						
7	# 10/F	WAIS-III	98						
8	# 11/F	WAIS-III	93						
9	# 12/M	WAIS-III	62						
10	# 13/F	WAIS-III	94						

EF, executive functioning; CC, complex cognition; SC, social cognition; EM, executive memory; PS, praxis speed; GNP, global neurocognitive performance.