Cognitive functioning in eighteen patients with cerebrotendinous xanthomatosis

A cognitive profile, measured over time

Master thesis

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ABSTRACT

Purpose: Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disease of bile acid synthesis and is treated with Chenodeoxylcholic acid (CDCA). Without medication, patients will develop progressive neurological symptoms. So far, little is known about cognitive functioning, therefore a cognitive profile will be documented.

Methods: Neuropsychological tests in eighteen CTX patients were assessed in various domains (intelligence, memory, attention and academic abilities). Results were described by percentile scores, based on existing norm scores. Cognitive changes over time were determined by reliable change index (RCI).

Results: All 18 CTX patients experienced attention deficits and most of them had mild problems with memory, intelligence, academic abilities and performance on a cognitive screening. Over time, this cognitive profile shows an improvement within the first years after medication, but a declination from low to disturbed afterwards.

Conclusion: Most of the patients showed a relatively normal development early in life and slowly developed neurological and cognitive symptoms. It is reasonable that because of accumulation of cholestanol in the brain over years, earlier diagnosis and medication might prevent further deterioration. Therefore, it is important to recognize CTX at an early stage and the resulting (neuro)psychological problems. Despite this relatively large CTX patient group, more research is needed to establish a more explicit cognitive profile and to provide more information about disease development and cognitive progression.

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disease of bile acid synthesis, which is caused by a pathologic mutation of the CYP27A1 gene. The clinical neurological presentations of CTX are variable. The initial symptoms typically start in childhood with chronic diarrhea and juvenile cataract. Progressive neurological deterioration follows in adolescence or adulthood with progressive spastic tetraparesis and cerebellar ataxia. These neurological signs are often accompanied by the appearance of tendon xanthomas, mainly on the Achilles' tendons [3]. In most untreated patients older than 50 years, ataxia, pyramidal signs and bilateral cataracts are present [12]. Little is known about causes of death in CTX-patients. One study of Barkhof et al. (2010) reported two patients who died of bronchopneumonia at age 54 and 45, which is not related to CTX, thus this was not the direct death cause [1].

This review reported over 300 identified patients with 50 different mutations in the CYP27A1 gene associated with CTX. This enzyme is involved in the synthesis of chenodeoxycholic and cholic acids from cholesterol. The metabolic block causes a progressive storage of cholestanol, which is produced by cholesterol. Cholestanol is accumulated in many tissues, including the brain, eyes and tendons [23]. Determination of deficits in gene mutations, cholesterol and cholestanol level in serum and level of bile alcohols in urine will confirm the clinical suspicion of the early symptoms [31]. Moreover, high cholestanol levels are very useful for diagnosis of CTX, but do not have a prognostic value (they do not correlate with severity). Additionally, normalization of cholestanol levels is not necessarily associated with clinical stabilization [25].

Synthetic chenodeoxylcholic acid (CDCA, Chenofalk or Xenbilox) is the primary treatment for CTX. It blocks the accumulation of cholestanol [3]. Other treatments include the use of a 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitor including Simvastatin, Pravastatin or Atorvastatin, in combination with chenodeoxycholic acid [31]. Although it is effective for normalizing the cholestanol level and stabilizes disease progression, it does not improved already existing neurological symptoms (A. Verrips, personal communication, 14 November 2012). Because the initial typical symptoms vary due to the overall effect of cholestanol accumulation, patients with CTX are usually not diagnosed until adulthood when neurological symptoms and xanthomas are already present and treatment is less effective. In most patients chenodeoxylcholic acid can stabilize disease progression and will prevent typical CTX complaints, for example xanthomas [3]. In a study of Berginer, Berginer, Korczyn & Tadmor

(1994), CDCA treatment resulted in neurological and biochemical improvement after two to three years [2].

Cholesterol metabolism is known to be involved in CTX, but also in atherosclerosis, vascular dementia (VD), possibly in the pathogenesis of Alzheimer's disease (AD)[15], cerebral vascular lesions, atherosclerotic parkinsonism and other cognitive deficits [7, 9-10]. The ratios of 27-hydroxycholesterol to cholesterol are similar in AD, VD, Mild Cognitive Impairment as in CTX, but significantly lower compared to non-demented subjects and depressed patients. Although, gender influences this ratio in that men have about 10% higher levels than women in a normal population [15], this ratio is equal in CTX patients [16].

Central nervous system atrophy and white matter changes in the brain as observed by Magnetic Resonance Imaging (MRI) are typical neuroradiological findings in CTX. In a study of Berginer et al. (1994), neither deterioration, nor improvement of focal findings were observed after two or three years of CDCA treatment [2]. Most severe lesions at MRI are found in the dentate nucleus of the cerebellum and basal ganglia [1, 5] and adjacent white matter. Besides, lesions in the internal capsula, brain stem and spinal cord are also seen. Atrophy is often found in the cerebellum, infratentorial region and in the study of Barkhof et al. (2010) in the medial part of the globus pallidus [1]. On MRI the distribution of the lesions is mostly consistent with the clinical presentation of pyramidal and cerebellar signs, mainly in a later stage of the disease. In contrast, Guerrera et al. (2010) found that cortical volume, rather than white matter volume was decreased in 24 patients and correlated closely with patients' clinical status ($r = -0.65$, $p < 0.001$) and Mini Mental State Examination score ($r = -0.58$, $p < 0.01$) [11]. This cortical atrophy and damage in major associative fiber tracts accounts for the broad spectrum of cognitive deficits that is observed and suggests impairment of higher cognitive functions, dementia and mental retardation [5].

Moreover, cognitive impairments are found in patients with CTX. Since the prevalence of CTX is estimated of 1 in 50.000 births, few patients are available for research. Therefore little is known about cognitive functioning in CTX patients [19, 23]. Current knowledge about cognitive functioning in CTX patients is mainly based on case studies, with only few larger studies (for an overview, see appendix I). CTX-patients initially show a normal cognitive development, but later on they demonstrate a slow cognitive regression and often develop learning disabilities or mental retardation. During adolescence or adulthood patients sometimes develop epilepsy [3], dementia, low intelligence, behavioral problems [23] or other cognitive deficits that can lead to severe handicap [3]. Guyant-Maréchal et al. (2005) reported

that 66% of the included 32 CTX-patients developed mental retardation or dementia [12], Verrips et al. (2000) confirmed this [30]. Another study described mental retardation and low intelligence in 81% of the 175 patients [23]. Early treatment can lead to psychiatric, cognitive and behavioral improvement. However, studies reporting a significant improvement of cognitive functioning after treatment are scarce. Mainly because treatment is less effective in later stages of the disease, when these symptoms are already present [3].

Two case studies [13, 24] described a total of seven children with CTX, some with disturbed mental functioning. After initiation of treatment these children showed a remarkable clinical improvement and a slightly higher intellectual quotient (IQ). But whereas the IQ of some children remained low average as compared to children of the same age, other children in this study had normal and stable cognitive development. Based on these studies, it is stated that early diagnosis of CTX and start of treatment during childhood can have a preventive effect on neurological deterioration for at least a period of five years. Other case reports present adult CTX-patients varying from normal functioning to severe intellectual disabilities, some with impaired general cognitive functions including memory and concentration, moderate mild retardation or comorbid severe psychiatric disorders, dementia, or Parkinsonism. Most of these studies describe, after various lengths of medical treatment, slight improvement in most adult patients in some domains, but some other studies found that cognitive functioning remained unchanged [3, 5, 7, 9-10, 14, 16-17]. However, Guyant-Maréchal et al. (2005) reported a CTX-patient with comorbid frontal dementia, behavioral symptoms and deterioration in global cognitive functions, executive functions and memory. During the first six months of medication, an improvement was observed. Despite medical treatment during three years, cognitive functions slowly deteriorated [12].

A summary of findings of the studies on cognitive functions in CTX is displayed in Table 2. In these previous studies a trend is described, however many limitations are found. Current knowledge about cognitive functioning in CTX patients is based mainly on case studies, with only one large series report of 24 patients [11]. Most of these studies included an intelligence test or MMSE (screening test) only. Case-studies that include other cognitive tests, report various findings in different areas of cognition. In all these studies no practice effects were taken into account, to correct for learning effects, due to repeated neuropsychological testing.

The current study will focus on a larger group of CTX patients and will take several cognitive areas into account, at varying time points. This research will establish a cognitive profile of the cognitive functions of this patient group, in which results of each test score will be compared with z-scores. With these individual z-scores a mean group z-score for the total group in every cognitive domain will be calculated. Furthermore correlations will be Based on the limited previous research, it is hypothesized that CTX patients will have a low intelligence level and deficits in attention, executive functions and memory. The expectation is that these different test scores will correlate with age, gender, age at diagnosis, time since diagnosis, education level and biochemical values. Additionally, individual results will be examined over time measured by reliable change index, corrected for practice effects. Patterns of decline, stabilization or improvement of cognitive domains will be visually examined. The expectation is that, because most of these patients receive medication directly after diagnosis, during the tests, their cognitive functions will remain stable.

METHODS

Patients

This neuropsychological study is part of a large neurological study in CTX patients. All patients were formally diagnosed by neurologists and were neuropsychologically tested in the University Medical Centre Radboud (UMC Radboud) and Canisius Wilhelmina hospital (CWZ); within a time span of 24 years, between 1989 and 2012. CTX-patients were included in the neuropsychological study after being referred for neuropsychological testing by a neurologist in the CWZ. All patients were seen in scope of standard care and participated the study on voluntary basis. Some patients already had a diagnosis of CTX, and visited their neurologist for having novel cognitive complaints. Other patients visited a neurologist for examination of cognitive complaints and were diagnosed with CTX after thorough medical examination.

Instruments

Demographics (gender, level of education, age) and medical history (age at diagnosis, biochemical values, genetic information, neuro-anatomic findings) were obtained by medical chart abstraction (Table 2). To measure cognitive functioning, a battery of neuropsychological tests was administered. These tests addressed intellectual abilities, memory, attention and academic abilities (visuoconstruction, naming, arithmetic and verbal fluency). In addition, a cognitive screening was administered, which measured orientation, memory, attention, language and visuoconstruction. All patients underwent different tests. Tests that had been administered in less than five patients were not taken into account (see Table 4.1 and 5 for an extensive overview).

Until 1996 eight patients were tested in scope of standard care by neurologists of UMC Radboud. A limited test battery was administered: Wechsler Adult Intelligence scale (WAIS-I), Wechsler Memory Scale (WMS-III), Stroop Color Word test and Mini Mental State Examination (MMSE). Since 2005, twelve patients (including two patients tested previously by the neurology department of the CWZ) were seen in scope of standard care by neuropsychologists in the CWZ. They underwent most of the subtests of a more extensive test battery, with a total of tests assessing more cognitive domains. For a detailed description of this test battery and the different subtests administered, see Tables 3, 4 and 5.

Procedure

Neuropsychologists in the UMC Radboud administered neuropsychological tests, after a brief intake with a neurologist. In patients who were seen in the CWZ, first an extensive intake was administered by a neurologist to determine cognitive symptoms. Afterwards, another intake was administered by a neuropsychologist. Neuropsychological tests were administered by undergraduate neuropsychology students, supervised by a senior neuropsychologist, with a duration of about three to four hours with a few resting periods provided in the meantime. After several weeks the results were discussed with the patient by the neurologist.

Statistical analysis

First patients will be described individually. Descriptive statistics were used to provide more general information about age, education level, gender, age at diagnosis, time between diagnosis and measurement, neurological, psychological and cognitive complaints. Biochemical values are classified by the neurologist in low, average, high (+) or too high (++). Cholestanol in these patients is average between 4.7 and 6.5 mmnol/l, cholesterol between 3.3 and 12.5 mmol/l and the cholestanol to cholesterol ratio (CCR) below 0.30. (A. Verrips, personal communication, 14 November 2011). Univariate Pearson's correlations among these variables and results of the neuropsychological tests were calculated. Patients were divided into three groups, according to years after start with medication. All different time point per patient were taken into account. For this study only tests that are administered in five patients or more, with clear normative data, were taken into account. With regard to the Wechsler Adult Intelligence Scale (WAIS), in most patients only a few subtests of the WAIS-I or WAIS-III were administered, in other patients the entire test was assessed. Of the other tests, same versions were used.

Furthermore, patients' results were transformed to z-scores based on mean and standard deviation. The z-scores were used to generate a classification of the performance on different cognitive domains per patient, based on mean and standard deviation (of the normative comparison group) (see Table 4.1 for test descriptives). According to this classification, patients' results were disturbed** (<2 standard deviation), low* (<1 standard deviation), average, high (>1 standard deviation) or gifted (>2 standard deviation). Some patients could not accomplish the Stroop task or Trailmaking Test, their score was set at -4 (two times lower than disturbed (-2)). Test scores were described and classified to a mean group z-

score. To calculate this mean, tests of the last test moment of every patient were used. In most domains every test will be used, but in the mean of intelligence only total, verbal and performal IQ will be taken into account. Graphs are presented per domain per patient.

Results will be examined over time within each individual with more test moments in tests with available norm scores over time. Reliable change in neuropsychological performance tests will be calculated by the reliable change index (RCI) reflecting change at the individual level in the context of observed changes in the control group [6]. Z-scores of each individual patient will be compared to all previous z-scores and marked if the results were significantly increased or decreased. Control group data were obtained from test manuals and articles. See Table 4.2 for an overview of the control group measurements. The subsequent formula was used [21], where r_{xy} reflects the test-retest reliability, X_{i1} and X_{i2} are the individual result at time point 1 and 2, Xc1 and Xc2 are the means and S^2_x and s^2_y the standard deviation of a control group in a particular time interval.

$$\frac{(X_{i2} - X_{i1}) - (X_{c2} - X_{c1})}{\sqrt{(S^2_x + S^2_y)\,(1 - r_{xy})}}$$

RESULTS

Patient characteristics

In this study eighteen CTX-patients were neuropsychologically tested between 1989 and 2012 in the Canisius Wilhelmina hospital and Radboud hospital in Nijmegen, the Netherlands. The group consisted of nine male and nine female patients, ranging in age from 31 to 58 years at time of testing, diagnosed between the age of 20 and 46. Most of the included CTX-patients were already diagnosed. The interval between diagnosis and the first test was six months up to 28 years. They were treated with Chenodeoxylcholic acid (CDCA), most of the time since diagnosis, often in combination with a HMG-CoA reductase inhibitor like Pravastatin. Three patients (8, 11 and 13) used no medication during the first test, 15 patients had used medication for 0 months up to 17 years. The interval between start medication and the first test was -1 up to 28 years. Neuropsychological tests were administered at different stages of the disease for different patients. Patients were seen several times, within unequal time intervals between the assessments (ranging from six months up to 15 years).

In the subsequent tables (Table 1.1 to 1.8) six families and seven individual patients will be described. These individual patients are not related to each other, due to similar test intervals or test batteries they are described together. Patient 3 and 4 were tested within a six months time interval; patient 7, 8 and 13 were tested once and 10 and 12 were tested thrice with an extensive test battery.

Table 1.1

Family 1: sister & brother

	Patient 1					Patient 2				
Age at diagnosis	44					36				
Gender	F					M				
Symptoms	Childhood: chronic diarrhea Typical CTX symptoms later: epileptic insults, cataract surgery, pyramidal + cerebellar symptoms, mental retardation, xanthomas					Typical CTX symptoms: pyramidal + cerebellar symptoms, xanthomas, mental retardation, cataract surgery, possibly epileptic seizure				
Social background	unknown					Education: two years secondary school Work: truck driver until 30, later sheltered workshop Living environment: independent				
Medication	anti-epileptic drugs, medication for cardiovascular and gastro-enterologic problems, tranquilizers, vitamin B immediately. CDCA one year after diagnosis					CDCA one year after diagnosis				
		0	**2**	**6**	**6.5**		**-1**	**2**	**6**	**6.5**
Test results at time since medication (in years)	**cognitive screening**			-1.5*	-1.5*	**cognitive screening**			0	-1*
	intelligence	-1.58*	-1.18*	-0.38	-0.38	**intelligence**	-0.71	-0.4	-0.5	0
	memory	-1.26*	-0.67	-2.02**	-1.67*	**memory**	-1.13*	-0.73	-2.51**	-1.18*
	attention			-3.25**	-2.80**	**attention**			-1.52*	-2.09**
Other	Better performance on visual, rather than verbal memory. Impatient, emotionally unstable, performance anxiety and lack of cooperation during the tests. In need to talk about CTX and consequences					Disturbed mental flexibility. Impatient during the tests.				

Table 1.2

Patient 3 & 4

	Patient 3			Patient 4		
Age at diagnosis	33			45		
Gender	M			M		
Symptoms	Typical CTX symptoms: polyneurpathy, xanthomas, typical parkinsonism, cerebellar and pyramidal symptoms (flat affect, poor mimic, stereotype movements, hypokinesia, rigid, slow and monotone speech, dysarthria) Other: myocardial infarction, depression, fatigue, hallucinations, attempted suicide			unknown		
Social background	Living environment: hospitalized in a psychiatric institution			unknown		
Medication	CDCA immediately after diagnosis, statins 16 years later			CDCA immediately after diagnosis		
Neuro-anatomic findings	MRI (27 years after medication): normal cerebral structures, no atrophy			unknown		
		14		unknown		
Biochemical values at time since medication (in years)	**cholestanol** **cholesterol** **CCR**	25++ 6.1 0.42%++				
		7	**7.5**		**12**	**13**
Test results at time since medication (in years)	**cognitive screening** **intelligence** **memory** **attention**	0.5 -0.63 -1.98* -0.58	-0.5 -0.25 -1.88* -0.92	**cognitive screening** **intelligence** **memory** **attention**	-3.5** -1.13* -2.58** -3.86**	**-3.5**** **-1.25*** **-2**** **-3.49****
Other	The neurologist assumed that the reason for his high cholestanol level is that he used another cholestanol reducing medicine than CDCA			Better performance on performal, rather than verbal tasks		

Table 1.3

Family 2

Family 2	Patient 5			Patient 6		
Age at diagnosis	34			41		
Gender	F			M		
Symptoms	unknown			unknown		
Social background	unknown			unknown		
Medication	CDCA and statins immediately after diagnosis			CDCA and statins immediately after diagnosis		
		13	**14**		**13**	**13.5**
Test results at time since medication (in years)	**cognitive screening** **intelligence** **memory** **attention**	-6** -2.13** -3.17** -3.88**	-5.5** -2** -2.98** -4.73**	**cognitive screening** **intelligence** **memory** **attention**	-2** -1.25* -1.8*	-3** -1.25* -2.37** -5.31**
Other				Better performance on performal, rather than verbal tasks		

Table 1.4

Patient 7, 8 & 13

	Patient 7	Patient 8	Patient 13
Age at diagnosis	F	M	39
Gender	31	34	F
Symptoms	Typical CTX symptoms in childhood: cataract surgery, diarrhea, no xanthomas Other: depression, psychological and psychosocial problems, asthma	Typical CTX symptoms: xanthomas and problems with speaking (tachylalia, dysarthria and word finding difficulties), mental retardation Other: depression, psychological and psychosocial problems	Typical CTX symptoms: chronic diarrhea, xanthomas, problems with speaking (tachylalia), in childhood a few (epileptic?) insults Other: fatigue, he was short-tempered and down
Social background	Education: secondary school Work: in production and cleaning Living environment: divorced, two children, lives independent	Education: primary school Work: sheltered workshop	Education: higher education Work: project account manager Living environment: together, independent

Medication	CDCA three years after diagnosis, statins, tranquilizers				CDCA and statins immediately after diagnosis, antidepressants				statins and medication for gastro-enterologic problems immediately after diagnosis. CDCA one year after diagnosis	
Neuro-anatomic findings	unknown				MRI (8 years after diagnosis): slight periphery neuropathy				MRI (at diagnosis): hyper intense changes, mainly central in the right cerebellum	
Biochemical values at time since medication (in years)	unknown					**8**	**10**		unknown	
					cholestanol	7+	8+			
					cholesterol	4.3	3.8			
					CCR	0.1	slightly high+			
		9				**12**				**-0.5**
Test results at time since medication (in years)					**cognitive screening**	-0.5				
	intelligence	-1.42*			**intelligence**	0.33			**intelligence**	-2.93**
	memory	-0.69			**memory**	-0.65			**memory**	-0.54
	attention	-1.04*			**attention**	0.56			**attention**	-4.17**
	academic abilities	-2.28**			**academic abilities**	0.44			**academic abilities**	-2.03**
Other	Performance on a visuoconstruction task and the subsequent visual memory tests was disturbed. Various results in attention (average to disturbed)				-				No hypercholesterolemia, but a normo- or hypocholesterolemia	

Table 1.5

Family 4: brother and sister

	Patient 9					Patient 11					
Age at diagnosis	30					25					
Gender	F					M					
Symptoms	Childhood: cataract, diarrhea Typical CTX symptoms later: neuropathy, cerebellar symptoms, problems with speaking, including tachylalia and dysarthria					Childhood: cataract, diarrhea Typical CTX symptoms later: neuropathy, cerebellar symptoms, problems with speaking, including tachylalia and dysarthria					
Social background	Work: home care and housekeeping Living environment: independent					Education: four years secondary school Work: nursing home, sheltered workshop Living environment: supervised					
Medication	CDCA and statins immediately after diagnosis					Statins immediately and CDCA 13 years after diagnosis					
Neuro-anatomic findings	MRI (11 years after diagnosis): a slight asymmetry of the ventricle system with a disadvantage to right and high signal activity central in both cerebellar hemispheres, which could correspond with lesions in CTX					MRI (15 years after diagnosis): Signal changes, severe atrophy in the cerebellum and minor supratentorial atrophy. Extended perivascular liquor regions and hyper intense signals on T2, also around basal nucleus					
		11	**13**	**13,5**	**15**		**16**	**16.5**			
Biochemical values at time since medication (in years)	**cholestanol**	1	6	10+	7+	**cholestanol**	14+	3			
	cholesterol	4.9	2.8	3	3	**cholesterol**	3.2	2			
	CCR	0.02	0.22	0.34	0.23	**CCR**	0.42+	0.15			
		0.5	**1**	**11**	**17**		**-0.5**	**0.5**	**5**	**13**	**15**
Test results at time since medication (in years)	**cognitive screening**	-2**	-4**			**cognitive screening**	0.5	1			
	intelligence	-0.63	-0.5	-1.06*	-2.04**	**intelligence**	-0.38	0	-2.04**	-1.87*	-1.94*
	memory	-1.4*	-1.13*	-0.80	-1.87*	**memory**	-1.49*	-1.27*			-1.88*
	attention	-0.97	-2.28**	-1.65*	-1.57*	**attention**	-2.89**	-3.41**			-16.12**
	academic abilities			-0.98	-0.94	**academic abilities**					-1.11*
Other	Their sister also had CTX, but she died a few years before the last test moment. Trivializing symptoms during intake					Better performance on performal, rather than verbal tasks					

Table 1.6

Patient 10 & 12

	Patient 10	Patient 12
Age at diagnosis	23	32
Gender	F	M
Symptoms	Typical CTX symptoms: pyramidal symptoms, epilepsy Other: rheumatoid arthritis, urine-incontinence, heart and psychological problems (possibly due to medication)	Typical CTX symptoms: cataract surgery, xanthomas, problems with speech, cerebellar symptoms, no diarrhea Other: fatigue, he was short-tempered and down
Social background	Work: cashier and caretaker, later incapacitated Living environment: together, independent	Education: secondary school Work: on voluntary basis and sheltered workshop

					Living environment: supervised with his parents					
Medication	CDCA and statins immediately after diagnosis				CDCA and statins immediately after diagnosis, medication for gastro-enterologic problems, muscle tranquilizers					
Neuro-anatomic findings	MRI (11 years after diagnosis): multiple white matter lesions supratentorial and in dendate nucleus				unknown					
Biochemical values at time since medication (in years)		**14**				**15**				
	cholestanol	7+			**cholestanol**	11+				
	cholesterol	3.3			**cholesterol**	3.1				
	CCR	0.11			**CCR**	normal				
		11	**12**	**14**		**1**	**10**	**15**		
Test results at time since medication (in years)	**intelligence**	-1.38*	-1.47*	-1.29*	**intelligence**	-1.04*	-2.11**	-1.84*		
	memory	-0.46	-0.39	-0.57	**memory**			-1.7*		
	attention	-2.06**	-1.09*	-1.24*	**attention**	-2.99**		-2.64**		
	academic abilities	-1.76*	-1.87*	-2.12**	**academic abilities**	-1.76*				
Other	Spinal CTX. Varying results in memory, attention and academic abilities				-					

Table 1.7

Family 5: sister and two brothers

	Patient 14					Patient 15						Patient 16				
Age at diagnosis	45					44						46				
Gender	F					M						M				
Symptoms	Typical CTX symptoms: mental retardation, problems with speech, cerebellar symptoms, cataract surgery, epilepsy, xanthomas, no diarrhea Other: behavioral problems, mood swings					Typical CTX symptoms: mental retardation, problems with speech, cerebellar symptoms, cataract surgery, diarrhea, xanthomas						Typical CTX symptoms: mental retardation, problems with speech, cerebellar symptoms, cataract surgery, epileptic insults, no xanthomas, angina pectoris, polyneuropathy				
Social background	Education: special primary education Work: sheltered workshop Living environment: supervised					Education: primary school Work: sheltered workshop Living environment: supervised						Education: special primary education Work: sheltered workshop Living environment: supervised				
Medication	CDCA and statins immediately after diagnosis. Antidepressants and anti-epileptic drugs until 1 year before tests					CDCA one year after diagnosis, statins, antidepressants and medication for cardiovascular problems						CDCA one year after diagnosis, statins, (muscle) tranquilizers, medication for cardiovascular and gastro-enterologic problems				
Genetic deficits						Compound heterozygote for two mutations in CYP271A gene						Two pathogenic mutations in both alleles of the CYP271A gene				
Neuro-anatomic findings	MRI (at diagnosis): high signal activity in cerebellum (in dentate nucleus)					MRI (one year after diagnosis): no typical CTX changes in the semiovale, but characteristic asymmetry						MRI (one year after diagnosis): minimal white matter lesions, according to age				
Biochemical values at time since medication (in years)		**1**	**2**	**2.5**	**5**		**0**	**1**	**1.5**	**2**	**4**		**1**	**1.5**	**2**	**4**
	cholestanol	29 ++	19 ++	15 ++	12+	**cholestanol**	low	39 ++	32 ++	19 ++	5	**cholestanol**	117 ++	20 ++	19 ++	6
	cholesterol	4.1	4.4	3.9	3.7	**cholesterol**	73 ++	2.8	3.9	3.2	2.7	**cholesterol**	-	3.2	3.3	3.5
	CCR	too high++	mini-mal	0.39+	0.32	**CCR**	-	1.38 ++	0.82 ++	0.59+ +	0.19	**CCR**	-	0.6	0.57 ++	0.17
			5					**4**						**4**		
Test results at time since medication (in years)	**cognitive screening**		-2.5**			**cognitive screening**		-2.5**				**cognitive screening**		-2.5**		
	intelligence		-3.04**			**intelligence**		-2.73**				**intelligence**		-2.93**		
	memory		-3.1**			**memory**		-2.9**				**memory**		-2.52**		
	attention		-1.17*			**attention**		-2.33**				**attention**		-1.09*		
	academic abilities		-2.82**			**academic abilities**		-1.43*				**academic abilities**		-2.67**		
Other	They have three brothers without CTX and one sister with CTX died because of an accident					-						-				

Table 1.8

Family 6: two sisters

	Patient 17					Patient 18			
Age at diagnosis	22					20			
Gender	F					F			
Symptoms	Typical CTX symptoms: polyneuropathy, cerebellar symptoms, speaking, vision and gastro-enterologic problems, urine-incontinence Other: fatigue, behavioral problems, pessimistic, short-tempered and in need to talk about this					Typical CTX symptoms: polyneuropathy, cerebellar symptoms, speaking , movement and gastro-enterologic problems Other: fatigue, obsessions			
Social background	Work: incapacitated Living environment: supervised					Work: incapacitated Living environment: together, independent			
Medication	CDCA and statins immediately after diagnosis					CDCA and statins immediately after diagnosis, muscle tranquilizers			
Neuro-anatomic findings	MRI (seven years after diagnosis): signal changes at the medulla oblongata, atrophy in the cerebellum (dentate nucleus)					MRI (seven years after diagnosis): lesions in cerebellum (dentate nucleus) and high signal activity in periventricular white matter			
Biochemical values at time since medication (in years)		**6**	**7**	**9**	**10**		6	9	10
	cholestanol	9+	<1	5	6	**cholestanol**	10+	6	7+
	cholesterol	3.5	4.6	2.9	3.3	**cholesterol**	5.25	3.9	4.7
	CCR	0.21	-	0.17	0.17	**CCR**	0.20	0.14	0.15
		13					**13**		
Test results at time since medication (in years)	**cognitive screening**	-2.5**				**cognitive screening**	**-1***		
	intelligence	-2.52**				**intelligence**	**-1.91***		
	memory	-1.15*				**memory**	**-1.67***		
	attention	-2.89**				**attention**	**-1.24***		
	academic abilities	**-1.01***				**academic abilities**	**-0.35**		

Overall results

Symptoms in this patient group were very varying. However, they all have typical CTX symptoms, such as xanthomas, (chronic) diarrhea (since childhood), (juvenile) cataract (surgery), problems with walking, speaking (tachylalia, dysarthria and word finding difficulties), epileptic insults, parkinsonism, cerebellar and pyramidal symptoms. Other non-related CTX symptoms in this patient group are fatigue, psychological, behavioral and cardiovascular problems. Most of these patients only completed special or normal primary school, four patients did (a few years of) secondary school and one patient (13) completed high school. Unless some data are missing, of 15 patients is known that they became mentally retarded, of which ten were working at a sheltered workshop or became incapacitated. Seven patients lived supervised and of six patients is known that they live independently, three together with a partner.

Mean group z-scores were calculated for different domains. Overall (see Table 3), results on a cognitive screening (-2.1) and attention (-3) were disturbed. Performances on intelligence (-1.6), memory (-1.74) and academic abilities (-1.01) were low. During the intake they all tended to trivialize their complaints, they reacted rather light-hearted and showed a lack of insight into their illness. During the test their motivation was low, some had performance anxiety or a lack of cooperation.

Neuro-anatomic findings, biochemical values and genetic deficits

These variables are associated with cognitive functioning: more sever neuro-anatomic deficits, higher biochemical values and genetic deficits causes more cognitive complaints. Neuro-anatomic findings were obtained in eleven patients. In two patients MRI-scans were age-appropriate and show no significant changes according to the normal population. In seven patients changes in the cerebellum (dendate nucleus), basal nucleus, basal ganglia, medulla oblongata, supratentorial and perivascular were observed. One patient (15) had no typical CTX changes, but characteristic asymmetry was noticed. Biochemical values were assessed in eleven patients. In most of these patients who received medication, biochemical values declined over time. Genetic deficits were identified in only two patients, where mutations were seen in the CYP271A gene.

Correlations

Univariate Pearson's correlations were calculated for the total group and patients were divided into three groups, according to years after start with medication (see Table 6). All different time points per patient were taken into account. Therefore the number of time points (N) is sometimes higher than the 18 included patients.

Lower results on a cognitive screening 4 to 10 years after medication were correlated with higher age (-0.85, $p < 0.01$), lower education level (0.82, $p < 0.01$) and higher age at diagnosis (-0.9, $p < 0.01$). More years of medication was correlated with lower scores in the total group (-0.51, $p < 0.05$), but within the 4 to 10 years after medication group, with higher scores (0.81, $p < 0.01$).

Higher intelligence scores were associated with lower age (-0.41, $p < 0.05$) and less years after start with medication (-0.47, $p < 0.05$) and only within 0 to 2 years after medication with a higher education level (0.77, $p < 0.01$).

Women (-0.35, $p < 0.05$) and younger patients (-0.49, $p < 0.01$) performed better on attention tasks in the total group and 11 to 17 years after medication (gender -0.67, $p < 0.01$, age -0.74, $p < 0.01$). This correlation was also seen for women within the first two years after start with medication (-0.86, $p < 0.05$).

Memory was correlated with lower age in the total group (-0.59, $p < 0.01$) and 11 to 17 years after medication (-0.67, $p < 0.01$); higher education level in the total group (0.55, $p < 0.01$) and 4 to 10 years after medication (0.86, $p < 0.01$); lower age at diagnosis in the total group (-0.4, $p < 0.05$) and 4 to 10

years after medication (0.64, $p < 0.05$); and more years of medication in the 4 to 10 years after medication group (0.73, $p < 0.05$).

Academic abilities were only correlated with higher education level, just in the total group. Bile acid levels (cholestanol, cholesterol and cholestanol to cholesterol ratio) were not correlated with cognitive test results.

Cognitive functioning over time

Nine patients (4 female, 5 male) were tested over time with an interval of six months to 16 years. Mean z-scores were used in graphs (see Figure 1). Overall, the results on these cognitive domains seemed to improve within the first years after medication, but declined from low to disturbed afterwards.

Reliable change indexes (RCI) were calculated to measure significant change. Means of each individual patient were compared to all previous means and marked if the results were significantly increased or decreased, according to the RCI (see Table 7). Due to a lack of available normative scores and control group data, only the Wechsler Memory Scale (WMS) and Stroop task were taken into account. Z-scores of the WMS were calculated from index scores and corrected for age, which might explain higher z-scores, while changes over time were declined. Four patients' results declined significantly within a time interval of one to 15 years, one patient remained stable within six months and the performance of one patient improved within six months. Three patients had varying results and the results of two of them overall declined in a time span of six months up to 17 years. Results at subtests are very diverse, but verbal memory capacities in many patients deteriorated and potentially as a result general memory also. Only one patient performed lower at delayed memory and all patients had stable results at an interference attention task.

Only patient 2 used no medication during the first test and was tested several times. His performance, corrected for reliable change, was low at general memory during the first tests, but average two years later. Another four years later his results declined. This was also seen in patient 1, who received medication at the first test moment. Patients 9 and 11 were also tested within the first years after receiving medication; their results were varying, but overall declined.

DISCUSSION

To our knowledge, this was the first study in which different cognitive domains in a relatively large CTX patient group have been examined (see Table 1). Symptoms in this patient group were very varying, as mentioned in previous studies [3, 12]. This study tended to provide a cognitive profile, the expectation was that CTX patients would have a low intelligence level and deficits in attention and memory. Overall, results on a cognitive screening and attention were disturbed. Due to low education level, performance on intelligence was low and as a result memory and academic abilities also. This study did not focus on executive functions, because of the low education level. Another expectation was that the different test scores would correlate with age, age at diagnosis, time since diagnosis and education level. Only a few clear, significant correlations were observed in this study, for example between age and memory, age and attention, education level and memory and age at diagnosis and memory. The last correlation is possibly influenced by age at test moment. Women tend to perform better at attention tasks in this patient group. Longer medication duration correlated once with higher results, but overall with lower results on cognitive domains. Within the first years it is possible that more years of medication can cause an improvement or stabilization of cognitive problems. However, later on, maybe due to a higher age, longer medication duration might correlate with lower cognitive results. The improvement was visible for 4 to 10 years and the declination for 11 to 17 years after medication, in this patient group

Bile acids were measured in only five to six patients and was not correlated with cognitive results. In most of the eight patients who received medication, biochemical values declined over time. Little is known about biochemical values, genetic deficits in this patient group and as a consequence only correlations and no clear conclusions could be drawn.

It was also hypothesized that, because most of the patients received medication directly after diagnosis, during the tests, their cognitive functions would remained stable. Many patients were tested within a few years after diagnosis. This cognitive profile shows, as Guyant-Maréchal et al. (2005) showed [12], an improvement within the first years after medication, but a decline from low to disturbed afterwards. The

results over time were corrected for practice effects with reliable change index and turned out to be varying, but overall declining.

Atrophy and white matter changes in CTX patients are varying. Seven patients do have the typical CTX changes, in the cerebellum (dendate nucleus), basal nucleus, basal ganglia, medulla oblongata, supratentorial and perivascular. One patient had no typical CTX changes, but characteristic asymmetry was noticed. Other MRI-scans are age-appropriate and show no significant changes according to the normal population. Nearly all patients in this patient group showed deficits in attention. One possible reason can be that attention is regulated by many different areas of the brain and in CTX patients these areas are affected because of the accumulation of cholestanol, spread throughout the brain.

The typical CTX changes in the brain can explain some symptoms, such as Parkinsonism, ataxia and problems with speaking [1, 5]. Cerebellar and pyramidal symptoms in these patients are also seen in Parkinson's disease. Both patient groups have MRI deficits in the cerebellum and basal ganglia, but the main focus is different: Parkinson's disease shows generally deficits in the substantia nigra and in CTX patients lesions are mainly concentrated in the cerebellum (dentate nucleus) and basal ganglia. The disease process is also comparable: first these physical symptoms develop and later cognitive problems are visible. However, patients with Parkinson's' disease sometimes develop dementia and have deficits in dopamine regulation. CTX patients often have a low intelligence level and most of them deteriorate into a mentally retarded level from adolescence by an accumulation of cholestanol and up to now, no patient in this group did develop dementia, despite similar ratios of 27-hydroxycholesterol to cholesterol in dementia [15].

Despite medication to stabilize the cholestanol accumulation, in one patient, MRI findings did not constantly improve, as also shown by Pilo-de-la-Fuente et al. (2011)[25]. Also found by Guyant-Maréchal et al. (2005) and observed in this patient group, it is supposed that diagnosis and medication later in the disease process will result in more symptoms and lower cognitive performances [12]. While the metabolic accumulation is reversible; however the resulting neurologic damage is not and already existing neurological damage does not improve [3].

Because of the accumulations of cholestanol, spread in the brain, it is to be expected that these patients have different symptoms. Due to this accumulation in their brain over years, most of these patients have a low intelligence level and may develop mental retardation. Due to this and neurological damage, normal aging, high age at start of medication (and more symptoms), these patients will have lower brain reserve,

which can cause more complaints and a more rapid degeneration (T. Balvers, personal communication, 14 August 2012). It appears to be that these patients show more cognitive deterioration, have more symptoms and as a result often mentally retarded, work at a sheltered workshop and live supervised.

The current study has some limitations. CTX is rarely diagnosed; therefore we were not able to include many patients. All patients have been measured within a large time span of 24 years, the interval between and number of assessments is not equal. Moreover the patients have been tested at different stages of their disease. Over the years all patients underwent different (sub)tests and versions. Therefore some tests were not included and statistical analysis of the group over time was not possible. Different tasks, within the cognitive screening, academic abilities and visual memory, were influenced by coordination problems of these patients; therefore these results can be lower than expected. It was difficult to use a control group, because of time restrictions and the intelligence level and comorbid symptoms, such as mental retardation and epilepsy. Therefore z-scores were used to compare these patients and compare tests of one individual at different moments. Norm scores were not properly comparable, because no Dutch control group was available, different control groups were used per test and the interval between the tests was about six months. In this group, the intervals were larger, thus less practice effects can be expected. As a result, the RCI is too strict for these intervals and with appropriate norm scores; there will be more significant changes in cognitive functions over time. Lemay et al. (2004) estimated an interval of 14 days, because in a longer period learning effect will be neutralized [18].

This study was initiated to provide a cognitive profile over time. Future research should focus on a larger population of CTX patients with shorter intervals and over a longer period of time. More domains should be assessed (for example executing functions) and patients' disease process has to be followed. Neuro-anatomic findings, biochemical values and genetic deficits should be taken into account. With these suggestions, it would be possible in the future to establish a more explicit cognitive profile and provide more information about disease development and cognitive progression.

As mentioned before in the literature, it is very important to diagnose CTX as early as possible [13, 24]. If a CTX-patient would be diagnosed at birth, they do have the genotype, but with medication, they would not develop the phenotype (A. Verrips, personal communication, 14 November 2012). Unfortunately, metabolism in children is different and it is not possible to measure biochemical values to diagnose CTX in this time (T. Balvers, personal communication, 14 August 2012). Therefore it is very important for every neurologist to be aware of the (un)typical symptoms of CTX in the early disease stage. Several patients in

this study had typical CTX symptoms in childhood, such as diarrhea, cataract or xanthomas. Others have not, but develop typical symptoms in adolescence or later in life. About 100 CTX-patients are known in the Netherlands now. However, this is expected to be underestimated, due to limited knowledge and delayed diagnosis. These unknown CTX-patients can still benefit from diagnosis and treatment. Their neurological symptoms can deteriorate and they will experience a better quality of life.

Furthermore, it is important to measure (neuro) psychological effects. Most of these patients have had unaccountable complaints for years and they and their families are relieved with the diagnosis and medication. However, they still have questions about life expectancy, what they can expect in the future and how the family has to deal with this disease and the resulting symptoms. Contact with fellow-sufferers and their families seems to be important here, for example a CTX-day just like in the Canisius Wilhelmina hospital (CWZ) every year. In general, the long term prognosis with medication is acceptable, life expectancy is normal. There is an experience with medical treatment since the nineteen eighties (A. Verrips, personal communication, 14 November 2012), so little is known about causes of death [1].

During the intake they all tended to trivialize their complaints, they reacted rather light-hearted and showed a lack of insight into their illness. During the test their motivation was low, some had performance anxiety or a lack of cooperation. Therefore it is very important to do an intake with family, caregivers or supervisors. Many CTX patients develop behavioral or mood problems and should be seen by a psychologist or psychiatrist.

In conclusion, nearly all CTX patients experience attention deficits and problems with memory, intelligence, academic abilities and performance on a cognitive screening, but appropriate to education level. This cognitive profile shows an improvement within the first years after medication, but a declination from low to disturbed afterwards. Most of these patients show a relatively normal development early in life and slowly develop neurological and cognitive symptoms. It is hypothesized that because of accumulations of cholestanol in the brain over years, earlier diagnosis and medication might prevent further deterioration. Therefore, it is important to recognize CTX at an early stage and the resulting (neuro)psychological problems, for advice and psycho-education. Despite this relatively large CTX patient group, there are still some unclarities.

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Table 2

Neuropsychological Studies about CTX

Author	Title	Number of patients	Age	Time interval	Conclusion
Bonnot et al., 2010 [3].	Cerebrotendinous xanthomatosis presenting with severe externalized disorder: improvement after one year of treatment with CDCA	2	18 (1) 22 (2)	1 year	Two CTX-patients with severe psychiatric disorders. A few weeks before treatment, one patient had borderline intelligence, difficulties with attention, inhibition, writing language and visual-spatial skills. After one year of treatment there was no difference in general cognitive function, but the other previously described impaired domains improved. The other patient had mild intellectual disability and deficits in processing speed, attention, inhibition, writing, visual spatial and mathematical abilities. After one year of treatment there was a slight improvement in all domains, except inhibition and some writing abilities, including information seeking.
Chang et al., 2010 [5]	Multi-parametric neuroimaging evaluation of cerebrotendinous xanthomatosis and its correlation with neuropsychological presentations	5	27-54	4 to 17 years	All patients had significantly lower scores on general intelligence and general cognitive performance compared to norm scores. Some were stable, other improved on general intelligence.
Fiorelli et al., 1990 [7]	Cerebrotendinous xanthomatosis: clinical and MRI study (a case report)	1	43	5 years	Dementia, parkinsonism and mild mental retardation since infancy, progressive deterioration of cognitive functions, MMSE 11/30.
Fuijyama et al., 1991 [9]	Parkinsonism in cerebrotendinous xanthomatosis	1	44	-	Slightly impaired cognitive abilities in a CTX-patient with parkinsonism.
Grandas et al., 2002 [10]	Letter to the editor: Early-onset parkinsonism in cerebrotendinous xanthomatosis	1	51	4 years	Patient with parkinsonism, mild global impairment and impaired intellectual capacities. After four years of treatment spasticity improved, but mental status, xanthomas, electrophysiological and MRI findings remained stable.
Guerrera et al., 2010 [11]	Clinical relevance of brain volume changes in patients with Cerebrotendinous xanthomatosis	24	15-62	1.9 - 3.2 years	A close relationship between decreasing values of MMSE and decreases in normalized brain volume and normalized cortical volume was seen.
Guyant-Maréchal et al., 2005 [12]	Unusual cerebrotendinous xanthomatosis with frontotemporal Dementia Phenotype	1	53	3 years	CTX-patients with frontotemporal dementia. Neuropsychological assessment revealed behavioral symptoms and deterioration in global cognitive functions, executive functions and memory. Cognitive functions improved within six months of treatment, but after three years it slowly progressively deteriorated, but no other signs of neurological deterioration appeared.
Heller et al., 2002 [14]	Zerebrotendinöse Xanthomatose. Eine behandelbare Stoffwechselerkrankung	2	42 (1) 46 (2)	-	Impaired intelligence, general cognitive functions, psychomotor retardation since school age (1) and deterioration of general cognitive functions, intellectual abilities, mainly concentration and memory, during five years (2).
van Heijst et al., 1997 [13]	Treatment and follow-up of children with cerebrotendinous xanthomatosis	5	7-20	2 years	Mental functioning of three children was disturbed, but after two years of treatment with CDCA their intellectual quotient (IQ) slightly improved. The other two patients had a normal IQ and this remained stable after treatment, but they showed a remarkable clinical and neurophysiological improvement.
Kuriyama et al., 1991 [16]	Cerebrotendinous xanthomatosis: clinical and biochemical evaluation of eight patients and review of the literature.	8	31-50	-	Five patients with low intelligence, two with normal intelligence and one with severe impaired mental abilities
Lee et al., 2002 [17]	Cerebrotendinous xanthomatosis with psychiatric disorders: report of three siblings and literature review	3	37-44	1.2 years	Three siblings with CTX and moderate to mild retardation. Their IQ was impaired and remained unchanged after 14 months of CDCA treatment (slightly improved in 2 patients).
Pierre et al., 2008 [24]	Prospective treatment of cerebrotendinous xanthomatosis with cholic acid therapy	2	6,5-8	5.5 years	Their cognitive development was initially mild delayed to normal. Repeated assessments have shown good progress, but their IQ remains low average for their age.

Table 3

Demographic characteristics and results

Patient		**1**				**2**				**3**		**4**		**5**		**6**		**7**	**8**	**9**			
Gender		F				M				M		M		F		M		F	M	F			
Year of diagnosis (age)		1988 (44)				1988 (36)				1988 (33)		1982 (45)		1981 (34)		1982 (41)		1998 (31)	1998	1995 (30)			
Medication		AED, CV, GE, Trs, vitamin B complex (1988), CDCA (1989)				CDCA (1989)				CDCA (1988), Statin (2004)		CDCA (1982)		CDCA, Statin (1981)		CDCA, Statin (1982)		CDCA (2001) Statin, Tr	CDCA (1998) AD,	CDCA (Apr 1995), Statin			
Year NPA (age)		Apr 1989 (45)	July 1991 (47)	Apr 1995 (51)	Oct 1995 (51)	Aug 1988 (36)	July 1991 (39)	Apr 1995 (43)	Oct 1995 (43)	Apr 1995 (40)	Sep 1995 (40)	June 1994 (57)	March 1995 (58)	June 1994 (47)	March 1995 (47)	June 1994 (53)	March 1995 (54)	2010 (43)	2010 (46)	Aug 1995 (31)	Feb 1996 (31)	2006 (41)	2012 (47)
Time since diagnosis (in years)		1	3	7	7	0	3	7	7	7	7	12	13	13	14	13	13	12	12	0,5	1	11	17
Time since medication (in years)		0	2	6	6	-	2	6	6	7	7	12	13	13	14	13	13	9	12	0,5	1	11	17
Cognitive screening (MMSE)	-2.1			**-1.5***	**-1.5***			**0**	**-1***	**0.5**	**-0.5**	**-3.5****	**-3.5****	**-6****	**-5.5****	**-2****	**-3****			**-2****	**-4****		
Intelligence mean	-1.6	**-1.58***	**-1.18***	**-0.38**	**-0.38**	**-0.71**	**-0.4**	**-0.5**	**0**	**-0.63**	**-0.25**	**-1.13***	**-1.25***	**-2.13****	**-2****	**-1.25***	**-1.25***	***-1.42****	***-2.93****	**-0.63**	**-0.5**	**-1.06***	***-2.04****
WAIS-I	VC			-0.5	-1*			-0.5	0	-0.5	-0.5	-2.5**	-2.5**	-2.5**	-2.5**	-2.5**	-2.5**	*-1.67**	*-2**	-1*	-1*	-1*	*-0.5*
WAIS-III	SI			-0.5	-0.5			0	0	0	0.5	-1.5*	-1.5*	-1.5*	-1.5*	-1*	-1*	*-1.67**	*-1**	0	0	0	*0*
	PC			0	0			-0.5	0.5	-1*	-0.5	-0.5	-0.5	-2.5**	-2.5**	-0.5	-0.5	*0.33*	*-0.5*	-0.5	-0.5	0	*0*
	BD			-0.5	0			-1*	-0.5	-1*	-0.5	0	-0.5	-2**	-1.5*	-1*	-1*	*-1.33**	*-0.5*	-1*	-0.5	0.5	*-0.5*
	VCI																	*-1.8**	*-2.67***				*-1.93**
	WMI																	*-1.33**	*-2.27***				
	POI																	*-1**	*-2.6***				*-2.33***
	PSI																	*-0.13*	*-3.2***				
	TIQ	-1.67*	-1.27*			-0.73	-0.4											*-1.47**	*-2.87***			-1.13*	*-2.07***
	VIQ	-1.2*	-0.93			-0.47	0											*-1.73**	*-2.93***			-1.13*	*-1.93**
	PIQ	-1.87*	-1.34*			-0.93	-0.8											*-1.07**	*-3***			-0.93	*-2.13***
Memory mean	-1.74	**-1.26***	**-0.67**	**-2.02****	**-1.67***	**-1.13***	**-0.73**	**-2.51****	**-1.18***	**-1.98***	**-1.88***	**-2.58****	**-2****	**-3.17****	**-2.98****	**-1.8***	**-2.37****	**-0.69**	**-0.54**	**-1.4***	**-1.13***	**-0.80**	**-1.87***
WMS-R	GM	-1.26*	-0.67	-2.26**	-1.67*	-1.13*	-0.73	-2.87**	-1.2*	-2.26**	-2.13**	-3.13**	-2.6**	-3.4**	-3.4**	-	-2.73**	-0.73	-3.13**	-1.53*	-1.33*	-0.8	-1.87*
	VeM			-1.4*	-0.93			-2.33**	-0.73	-2.07**	-2**	-2.27**	-2.2**	-2.87**	-2.93**	-2.2**	-2.53**	-0.16	-2.13**	-1.33*	-1.47*	-1.07*	-2**
	ViM			-2.4**	-2.4**			-2.33**	-1.6*	-1.6*	-1.5*	-2.4**	-1.4*	-3.33**	-2.53**	-0.93	-1.27*	-0.73	-3**	-1.33*	-0.6	0	-2**
	DM											-2.53**	-1.8*	-3.07**	-3.07**		-2.93**	-1*	-2.27**			-1.67*	-1.6*
VLGT	tot																	-0.5	-2**			-1.5*	
	lspd																	-0.5	-1*			-1*	
	vspd																	0.5	1.5			0.5	
	cons																	1	1.5			-1*	
	rec																	0	0.5			1	
	fpos																	0	1.5			0	
	ST																	0	1			0.5	
	LT																	-0.5	1			0	
Rey figure test	IR																	-3.3**				-2.9**	
	DR																	-3.67**				-3.22**	
Attention mean	-3			**-3.25****	**-2.80****			**-1.52***	**-2.09****	**-0.58**	**-0.92**	**-3.86****	**-3.49****	**-3.88****	**-4.73****		**-5.31****	**-1.04***	**-4.17****	**-0.97**	**-2.28****	**-1.65***	**-1.57***
WMS-R	C			-1.67*	-2.4**			-1.4*	-1.73*	-3.27**	-3.07**	-2.47**	-2.67**	-3.4**	-3.4**		-2.27**	-1.27*	-3.4**	-2.53**	-2.73**	-2.53**	-2.6**
Stroop	1			-2.13**	-1.25*			-1.38*	-0.13	1.13	1	-3.5**	-4.63**	-6.34**	-7.33**		-4.44**	-3.43**	-8.57**	0.71	-6.14**	-1.6*	0.15
	2			-2.55**	-1.19*			-0.75	-0.58	-0.17	0.25	-7.46**	-5.69**	-6.73**	-6**		-6.67**	-2.56**	-4.36**	-0.78	-3.44**	-1.89*	-1.44*
	3			-6.26**	-4.89			-2.24**	-4**	-0.28	-0.68	-5.06**	-3.94**	-3**	-5.79**		-6.83**	-0.94	-5.27**	-1.29*	-0.18	-0.76	-1.89*
	int			-3.62**	-4.26			-1.81*	-4**	-0.3	-2.09**	-0.54	-0.51	0.07	-1.11*		.33**	0.33	-1.71*	-0.94	1.08	0.33	-0.95
Bourdon	time																	-1.75*	-3.98**			-3.69**	
	om																	1.29	-2.29**			0.29	
TMT	A																	-1*	-4.13**			-1.91*	-1.8*
	B																	-0.77	-4**			-3.09**	-2.48**
	b-a																	-0.28	-4**			-1.67*	-1.52*
Academic abilities mean	-1.01																	**-2.28****	**-2.03****			**-0.98**	**-0.94**
Rey figure test	copy																	-12.33**				-1.67*	
Boston																		0.73	-3.99**			-0.7	-1.03*
GIT	calc																	-0.87	-2.42**			-1.31*	-1.53*
	flu1																	1.22	0.19			-0.69	-0.69
	flu2																	-0.17	-1.9*			-0.52	-0.52

Table 3 continued

Patient		10			11					12			13	14	15	16	17	18
Gender		F			M					M			F	F	M	M	F	F
Year of diagnosis (age)		1993 (23)			1982 (25)					1996 (32)			2011 (39)	2007 (45)	2007 (44)	2007 (46)	1999 (22)	1999 (20)
Medication		CDCA, Statin (1993)			CDCA (Apr 1995), Statin					CDCA, Statin (1996) GE, mTr			GE, Statin, soon CDCA	CDCA (2007), AD, AED (until 2011), Statin	CDCA (2008), AD, CV, Statin	CDCA (2008), CVs, GE, (m)Tr, lactulose, Statin	CDCA, Statin (1999)	CDCA, Statin (1999), mTr
Year NPA (age)		2004 (34)	2005 (35)	2007 (37)	march 1995 (37)	oct 1995 (38)	2000 (43)	2008 (51)	2010 (53)	1997 (33)	2006 (42)	2011 (47)	2012 (40)	2012 (50)	2012 (49)	2012 (51)	2012 (45)	2012 (43)
Time since diagnosis (in years)		11	12	14	13	14	19	26	28	1	10	15	1	5	5	5	13	13
Time since medication (in years)		11	12	14	-	0,5	5	13	15	1	10	15	-	5	4	4	13	13
Cognitive screening	Mmse				**0.5**	**1**							**-0.5**	**-2.5****	**-2.5****	**-2.5****	**-2.5****	**-1***
Intelligence mean		**-1.38***	**-1.47***	**-1.29***	**-0.38**	**0**	**-2.04****	**-1.87***	***-1.94****	**-1.04***	***-2.11*****	***-1.84****	***0.33***	***-3.04*****	***-2.73*****	***-2.93*****	***-2.52*****	***-1.91****
WAIS-I	VC	-1*	-1.5*	-2.5**	-0.5	0			*-1**	-1.5*	*-1.67**	*-1**	*0.67*	*-3***	*-2.67***	*-3***	*-2***	*-2.67***
WAIS-III	SI	-0.5	-1*	0.5	0	1			*-1.33**	0	*-2***	*-2***	*2***	*-3***	*-2.33***	*-2.33***	*-2.33***	*-2.67***
WISC	PC	0	-0.5	-1*	-0.5	-0.5			*-2.67***	-0.5	*-2.67***	*-2.67***	*0.67*	*-2.67***	*-3***	*-3***	*-2.67***	*-1.67**
	BD	-0.5	-1*	-0.5	-0.5	-0.5			*-2.33***	-0.5	*-1.67**	*-1.33**	*0*	*-2***	*-2***	*-3***	*-3***	*-1.33**
	VCI								*-0.47*		*-1.93**	*-1.4**	*0.4*	*-3.2***	*-2.4***	*-2.67***	*-2.13***	*-2.4***
	WMI								*-0.2*		*-1.6**	*-1.33**	*-0.47*					
	POI								*-2.6***		*-2.47***	*-2.07***	*0.33*	*-2.87***	*-3***	*-2.87***	*-2.47***	*-1.67**
	PSI								*-3.33***		*-2.2***	*-2***	*1.33**					
	TIQ	-1.47*	-1.6*	-1.4*							*-2.07***	*-1.73**	*0.27*	*-3***	*-2.67***	*-2.87***	*-2.53***	*-1.93**
	VIQ	-1.33*	-1.87*	-1.4*			-0.6	-0.8	*-0.8*	-0.6	*-1.67**	*-1.8**	*0*	*-3.2***	*-2.33***	*-2.73***	*-2.27***	*-2***
	PIQ	-1.33*	-0.93	-1.07*			-3.47**	-2.93**	*-3.07***	-1.47*	*-2.6***	*-2***	*0.73*	*-2.93***	*-3.2***	*-3.2***	*-2.75***	*-1.8**
Memory mean		**-0.46**	**-0.39**	**-0.57**	**-1.49***	**-1.27***			**-1.88***			**-1.7***	**-0.65**	**-3.1****	**-2.9****	**-2.52****	**-1.15***	**-1.67***
WMS	GM	-1.2*	-1.53*	-0.93	-1.47*	-1.2*			-2.47**			-1.93*	-1*	-3.4**	-3.4**	-2.8**	-1.33*	-1.73*
	VeM	-1.2*	-1.33*	-1.13*	-1.13*	-1.47*			-2.4**			-1.73*	-0.8	-3.27**	-3.27**	-1.87*	-1.73*	-2.07**
	ViM	-0.8	-1.33*	-0.13	-1.87*	-1.13*			-1.13*			-1.27*	-0.13	-2.73**	-1.67*	-2.87**	-0.2	-0.73
	DM	-1.07*	-1.13*	-1.33*					-1.53*			-1.87*	-0.87	-3**	-3.27**	-2.53**	-1.33*	-2.13**
VLGT	tot	-2**	-2**	-2**									0					
	lspd	-1*	-1*	-2**									0					
	vspd	2	1.5	1									0					
	cons	-2**	-2**	-3.5**									-2**					
	rec	1.5	2	2.5									0.5					
	fpos	2	1.5	0.5									0					
	ST	1.5	1.5	-0.5									-0.5					
	LT	1.5	2.5	1.5									-1.5*					
Rey figure test	IR	-2.67**	-2**	-2.78**									-1.6*					
	DR	-3**	-2.11**	-3.11**									-1.22*					
Attention mean		**-2.06****	**-1.09***	**-1.24***	**-2.89****	**-3.41****			**-16.12****	**-2.99****		**-2.64****	**0.56**	**-1.17***	**-2.33****	**-1.09***	**-2.89****	**-1.24***
WMS-R	C	-2.33**	-2.87**	-1.4*	-2.07**	-1.27*			-0.73			-1.87*	0.13	-3.4**	-1.87*	-2.33**	-1.8*	-1.33*
Stroop	1	-1*	-2.29**	-2**	-5**	-5**			-7.57**				1.38	1.38	0.89	0.22	-3.14**	-1.75*
	2	-1.78*	-1.11*	-1.44*	-2.1**	-3.1**			-4.09**				1.11	1.11	-0.15	0.08	-1.4*	-2.1**
	3	-1.89*	-0.56	-1.74*	-3.37**	-5.21**			-6.05**				0.08	0.08	-4**	-0.13	-1.5*	-3.55**
	int	-0.72	0.11	-0.85	-1.87*	-2.46**			-2.26**				0.44	0.44	-4**	-0.58	-0.64	-1.88*
Bourdon	time	0.34	0.34	1.06					-90.31**	-3.55**			0.96					
	om	-2.86**	-1.29*	-1.29*					-9.36**	-2.43**			1.57					
TMT	A	-1.1*	-1.9*	-0.7					-13.5**			-6**	-0.5	-0.93	-1.53*	-2.5**	-6.64**	0.36
	B	-4.92**	-1.16*	-2.15**					-20.4**			-2.59**	-0.09	-4**	-4**	-2.4**	-4**	0.04
	B-A	-4.36**	-0.21	-1.88*					-6.93**			-0.11	0.5	-4**	-4**	-1.04*	-4**	0.29
Academic abilities mean		**-1.76***	**-1.87***	**-2.12****					**-1.11***	**-1.76***			**0.44**	**-2.82****	**-1.43***	**-2.67****	**-1.01***	**-0.35**
Rey figure test	copy	-1*	-3.67**	-5**									0.33					
Boston		-4.41**	-3.13**	-2.7**					-0.5				-0.41	-7.69**	-4.29**	-6.13**	-0.86	-0.97
GIT	calc	-1.76*	-1.98*	-1.53*					-1.98*	-1.76*			-1.09*	-0.87	-1.76*	-1.76*	-0.87	-0.04
	flu1	-0.40	-0.04	-0.84					-0.25				1.81	-0.99	0.34	-0.54	-1.43*	0.46
	flu2	-1.21*	-0.52	-0.52					-1.72*				1.55	-1.72*	0	-2.24**	-0.86	-0.86

Mean group z-scores Z-scores: disturbed = < -2**, low = -1.99 –-1*, average = -.99–0.99, high = 1-1.99, gifted = > 2. NPA: Neuropsychological Assessment; Medication: AD: antidepressant medication, AED: Anti epileptic drugs, CDCA: Synthetic chenodeoxylcholic acid, CV: cardiovascular medication, GE: gastro-enterologic medication, (m)Tr: (muscle) tranquilizers, Statin: (HMG)-CoA reductase inhibitor; Cognitive screening: MMSE: Mini Mental State Examination; Intelligence: WAIS: Wechsler Adult Intelligence Scale (part I or III) subtests: VC: Vocabulary, SI: Similarities, PC: Picture Completion, BD: Block Design; domains: VCI: Verbal Comprehension Index, Work Memory Index: WMI, POI: Perceptual Organization Index, PSI: Perception Speed Index, TIQ: Total Intelligence Quotient, VIQ: Verbal Intelligence Quotient, PIQ: Perceptual Intelligence Quotient; WISC-R: Wechsler Intelligence Scale For Children–Revised; Memory: WMS-R: Wechsler Memory Scale - Revised, subtests: GM: General Memory, VeM: Verbal Memory, ViM: Visual Memory, DM: Delayed Memory; VLGT: Verbale Leer- & Geheugentaak (Verbal Learning & Memory Task in Dutch) subtests: tot: total score, lspd: read speed, vspd: forget speed, cons: consolidation, recog: recognition, fpos: false positives, ST: short term memory, LT: long term memory; Rey: Rey Figure test, subtests: Copy, IR: Immediate Recall, DR: Delayed Recall; Attention: WMS-R, subtest C: Concentration; Stroop: Stroop task, subtests 1: Reading, 2: Naming, 3: Interference, int: Interference score; Bourdon: Bourdon Wiersema test, calculated by time: time per row, om: omissions (om); TMT: Trail Making Test, part A, B, B-A: interference score; Academic abilities: Boston: Boston Naming test; GIT: Groninger Intelligentie Test (Dutch intelligence test), subtests calc: calculation, flu1 & flu2: fluency.

Table 4.1

Test overview

Tests	Domains	Test variables	Mean (SD) control group, to calculate z-scores
Cognitive screening			
Mini Mental State Examination (MMSE) [8]	- total score of cognitive screening	- total score of cognitive screening	28 (2) [8]
Intelligence			
Wechsler Adult Intelligence Scale (WAIS-I or WAIS-III) Wechsler Intelligence Scale for Children (WISC) [32]	- learned knowledge - abstract reasoning - visual differentiation - visuoconstruction - total, verbal and performal intelligence quotient	- Vocabulary (Vo) - Similarities (Si) - Picture Completion (PC) - Block Design (BD) - Total IQ (TIQ) - Verbal IQ (VIQ) - Performal IQ (PIQ)	100 (15) [32]
Memory			
Wechsler Memory Scale (WMS-III) [33]	- General Memory - Verbal Memory - Visual Memory Delayed Recall	- General Memory (GM) - Verbal Memory (VeM) - Visual Memory (ViM) - Delayed Recall (DR)	100 (15) [33]
Verbale Leer- en Geheugentaak (VLGT) [22]	- learning curve - short term verbal memory - long term verbal memory - recognition	- TOT_A - Recog - RtrKTm - LtrLTm	normscores converted into z-scores with manual [22]
Rey Figure Test [29]	- immediate visual memory - delayed visual memory	P_IR P_DR	z-scores calculated with manual, different per age [29]
Attention			
Wechsler Memory Scale (WMS-III) [33]	- Attention / Concentration	- Attention / Concentration (C)	100 (15) [33]
Stroop Color Word task (Stroop) [28]	- selective attention - divided attention	- P_time card 1 - P_time card 2 - P_time card 3 - P_3>2	z-scores calculated with manual, different per age, gender and education level [28]
Bourdon-Wiersma task [4]	- sustained attention	- Bourdon_sec_average - Bourdon_ommisions	men 14.47 (1.39) women 14.19 (0.7) man 22 (7) women 25 (7) [4]
Trail making test A+B [26]	- selective attention - divided attention	- P_TMTA - P_TMTB - P_TMTB-A	z-scores calculated with manual, different per age and education level [26]
Academic abilities			
Rey Figure Test [29]	- visuoconstruction	P_Copy	z-scores calculated with manual, different per age [29]
Boston Naming test [27]	- naming	- Boston_percentile	z-scores calculated with manual, different per age and education level [22]
Groningen Intelligence Test-2 (GIT-2) [20]	- arithmetic - verbal fluency	- GIT_calculation_percentile - GIT_fluency1_percentile - GIT_fluency2_percentile	10.9 (4.5) 20.7 (6.8) 16 (5.8) [20]

Table 4.2

Reliable Change Index, control group information

Wechsler Memory Scale (WMS) [33]			
Control group (n = 48): age 20 to 24 years, interval 4 to 6 weeks Used for patients between 31 and 39 years			
	T1 Mean (SD)	**T2 Mean (SD)**	**Test-retest reliability**
WMS GM	129.2 (18.4)	148.1 (17.2)	**.74**
WMS VeM	73.3 (15.5)	89.2 (14)	**.70**
WMS ViM	55.9 (7)	58.9 (6)	**.70**
WMS C	73.7 (11.8)	77.7 (12.3)	**.89**
WMS DR	79.6 (12.5)	91.5 (10)	**.72**
Control group (n = 53): age 55 to 64 years, interval 4 to 6 weeks Used for patients between 40 and 58 years			
	T1 Mean (SD)	**T2 Mean (SD)**	**Test-retest reliability**
WMS GM	108.3 (17.2)	127.6 (16.9)	**0.77**
WMS VeM	62.2 (12.4)	75.9 (12.8)	**0.69**
WMS ViM	46.2 (7.7)	51.7 (7.2)	**0.59**
WMS C	64.7 (10.2)	65.4 (10.2)	**0.88**
WMS DR	66.1 (13.1)	75.7 (13.2)	**0.74**
Stroop Color Word task [18][28]			
Controlgroup (n = 37): age 50 to 80 years, education level 6 to 22 years, interval 2 weeks			
	T1 Mean (SD)	T2 Mean (SD)	**Test-retest reliability**
Stroop reading	45.05 (6.39)	44.67 (6.78)	**0.73**
Stroop naming	67.87 (9.33)	64.99 (9.93)	**0.79**
Stroop interference	**140.15 (31.71)**	**119.56 (24.71)**	**0.77**

Table 5

Test battery since 2005, psychology department CWZ

- Wechsler Memory Scale-III (WMS-III)
- Wechsler Adult Intelligence Scale (WAIS-III)
- Stroop Color Word task
- Mini Mental State Examination (MMSE)
- Boston Naming Test
- Groninger Intelligentie Test-2 (GIT-2) (Calculation & Fluency)
- Trailmaking Test A+B

Optional:

- Verbale Leer- en Geheugentaak (VLGT) + recall
- Rey Figure Test (copy, immediate + delayed recall)
- Bourdon-Wiersma task
- Dictation & Reading test
- House & Bicycle drawing
- Symptom Checklist (SCL)
- Beck Depression Inventory (BDI)

Table 6

Correlations

Total	**gender**		**age**		**education level**		**age at diagnosis**		**time since medication**		**cholestanol**		**cholesterol**		**cholestanol to cholesterol ratio (CCR)**	
	N		N		N		N		N		N		N		N	
cognitive screening	21	0.42	21	-0.35	21	0,41	21	-0.24	21	-0.51*	-	-	-	-	-	-
intelligence	38	0.36	38	-0.41*	38	0,32	38	0.001	38	-0.47*	6	-0.45	6	0.46	5	-0.86
memory	36	-0.2	36	-0.59**	36	0.55**	36	-0.4*	36	-0.16	6	-0.42	6	0,43	5	-0.85
attention	33	-0.35*	33	-0.49**	33	-0.22	33	0.04	33	-0.32	6	-0.52	6	0.33	5	0.09
academic abilities	15	-0.24	15	-0.1	15	0.53*	15	-0.29	15	0.02	5	-0.85	5	0.33	5	-0.74

0-2y after medication	**gender**		**age**		**education level**		**age at diagnosis**		**time since medication**	
	N		N		N		N		N	
cognitive screening	5	0.79	5	0.79	5	0.78	5	-0.28	5	-0.56
intelligence	10	0.19	10	-0.31	10	0.77**	10	-0.5	10	-0.31
memory	9	-0.22	9	0.49	9	0.03	9	0.64	9	0.36
attention	6	-0.86*	6	0.01	6	0.13	6	0.75	6	-0.46
academic abilities		-		-		-		-		-

4-10y after medication	**gender**		**age**		**education level**		**age at diagnosis**		**time since medication**	
	N		N		N		N		N	
cognitive screening	9	0.37	9	-0.85**	9	0.82**	9	-0.9**	9	0.81**
intelligence	12	-0.04	12	-0.35	12	0.46	12	-0.24	12	0.37
memory	11	-0.13	11	-0.45	11	0.86**	11	-0.64*	11	0.73*
attention	12	0.07	12	-0.24	12	-0.31	12	0.13	12	0.1
academic abilities	4	0.46	4	-0.21	4	0.02	4	-0.12	4	-0.09

11-17y after medication	**gender**		**age**		**education level**		**age at diagnosis**		**time since medication**	
	N		N		N		N		N	
cognitive screening	7	0.27	7	-0.05	7	0.6	7	-0.31	7	-0.46
intelligence	16	-0.01	16	-0.06	16	-0.28	16	0.21	16	-0.21
memory	16	-0.16	16	-0.67**	16	0.39	16	-0.49	16	-0.45
attention	15	-0.67**	15	-0.74**	15	-0.22	15	-0.42	15	-0.13
academic abilities	9	-0.2	9	0.47	9	-0.19	9	-0.21	9	0.28

* $p < 0.05$, ** $p < 0.01$ N = number of time points

Table 7

Changes over Time in Z-scores, Calculated by Reliable Change Index (RCI)

Patient	**1**				**2**				**3**		**4**		**5**		**6**		**9**				**10**			**11**		
Gender	F				M				M		M		F		M		F				F			M		
Year of diagnosis	1988 (44)				1988 (36)				1988 (33)		1982 (45)		1981 (34)		1982 (41)		1995 (30)				1993 (23)			1982 (25)		
Medication	AED, CV, GE, Trs, vitamin complex (1988), CDCA (1989)				BCDCA (1989)				CDCA (1988), Statin (2004)		CDCA (1982)		CDCA, Statin (1981)		CDCA, Statin (1982)		CDCA (Apr 1995), Statin				CDCA, Statin (1993)			Chenofalk (1995), Zocor		
Year NPO (age)	1989 (45)	1991 (47)	1995 (51)	1995 (51)	1988 (36)	1991 (39)	1995 (43)	1995 (43)	1995 (40)	1995 (40)	1994 (57)	1995 (58)	1994 (47)	1995 (47)	1994 (53)	1995 (54)	1995 (31)	1996 (31)	2006 (41)	2012 (47)	2004 (34)	2005 (35)	2007 (37)	1995 (37)	1995 (38)	2010 (53)
Time since diagnosis (in years)	1	3	7	7	0	3	7	7	7	7	12	13	13	14	13	13	0,5	1	11	17	11	12	14	13	14	28
Time since medication (in years)	0	2	6	6	-1	2	6	6	7	7	12	13	13	14	13	13	0,5	1	11	17	11	12	14	0	1	15
Memory total	**-1.26***	**-0.67**	**-2.02****	**-1.67***	**-1.13***	**-0.73**	**-2.51****	**-1.18***	**-1.98***	**-1.88***	**-2.58****	**-2****	**-3.17****	**-2.98****	**-1.8***	**-2.37****	**-1.4**	**-1.13**	**-0.80**	**-1.87***	**-0.46**	**-0.39**	**-0.57**	**-1.49***	**-1.27***	**-1.88***
WMS-R, GM	-1.26*	-0.67	-2.26**	-1.67*	-1.13*	-0.73	-2.87**	-1.2*	-2.26**	-2.13**	-3.13**	-2.6**	-3.4**	-3.4**	-2.27**	-2.73**	-1.53*	-1.33*	-0.8	-1.87*	-1.2*	-1.53*	-0.93	-1.47*	-1.2*	-2.47**
VeM			-1.4*	-0.93			-2.33**	-0.73	-2.07**	-2**	-2.27**	-2.2**	-2.87**	-2.93**	-2.2**	-2.53**	-1.33*	-1.47*	-1.07*	-2**	-1.2*	-1.33*	-1.13*	-1.13*	-1.47*	-2.4**
ViM			-2.4**	-2.4**			-2.33**	-1.6*	-1.6*	-1.5*	-2.4**	-1.4*	-3.33**	-2.53**	-0.93	-1.27*	-1.33*	-0.6	0	-2**	-0.8	-1.33*	-0.13	-1.87*	-1.13*	-1.13*
DM											-2.53**	-1.8*	-3.07**	-3.07**		-2.93**			-1.67*	-1.6*	-1.07*	-1.13*	-1.33*			-1.53*
Attention total			**-3.25****	**-2.80****			**-1.52***	**-2.09****	**-0.58**	**-0.92**	**-3.86****	**-3.49**	**-3.88****	**-4.73****		**-5.31****	**-0.97**	**-2.28****	**-1.65***	**-1.57***	**-2.06****	**-1.09***	**-1.24***	**-2.89****	**-3.41****	**-16.12****
WMS-R, C			-1.67*	-2.4**			-1.4*	-1.73*	-3.27**	-3.07**	-2.47**	-2.67**	-3.4**	-3.4**		-2.27**	-2.53**	-2.73**	-2.53**	-2.6**	-2.33**	-2.87**	-1.4*	-2.07**	-1.27*	-0.73
Stroop, 1			-2.13**	-1.25*			-1.38*	-0.13	1.13	1	-3.5**	-4.63**	-6.34**	-7.33**		-4.44**	0.71	-6.14**	-1.6*	0.15	-1*	-2.29**	-2**	-5**	-5**	-7.57**
2			-2.55**	-1.19*			-0.75	-0.58	-0.17	0.25	-7.46**	-5.69**	-6.73**	-6**		-6.67**	-0.78	-3.44**	-1.89*	-1.44*	-1.78*	-1.11*	-1.44*	-2.1**	-3.1**	-4.09**
3			-6.26**	-4.89**			-2.24**		-0.28	-0.68	-5.06**	-3.94**	-3**	-5.79**		-6.83**	-1.29*	-0.18	-0.76	-1.89*	-1.89*	-0.56	-1.74*	-3.37**	-5.21**	-6.05**
Int			-3.62**	-4.26**			-1.81*		-0.3	-2.09**	-0.54	-0.51	0.07	-1.11**		-6.33**	-0.94	1.08	0.33	-0.95	-0.72	0.11	-0.85	-1.87*	-2.46**	-2.26**

Decreased and increased with regard to all the previous marked z-scores

Z-scores: disturbed = < -2**, low = -1.99 –-1*, average = -.99–0.99, high = 1-1.99, gifted = > 2.
Memory: WMS-R = Wechsler Memory Scale - Revised, subtests: GM = General Memory, VeM = Verbal Memory, ViM = Visual Memory, DM = Delayed Memory;
Attention: WMS-R, subtest C = Concentration; Stroop = Stroop task, subtests 1 = Reading, 2 = Naming, 3 = Interference, int = Interference score;

Figure 1

Cognitive Results over Time (in years after diagnosis)