Pituitary disorders and their extra-pituitary implications : observations in patients with nonfunctioning pituitary macroadenoma and the IGSF1 deficiency syndrome

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CHAPTER 9

Mild deficits in attentional control in patients with the IGSF1 deficiency syndrome

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ABSTRACT

Objective

Male patients with the X-linked IGSF1 deficiency syndrome are characterized by central hypothyroidism, delayed pubertal testosterone rise, adult macroorchidism, variable prolactin deficiency and occasionally transient partial growth hormone deficiency. Thyroid hormone plays a vital role in brain development and functioning, and while most patients receive adequate replacement therapy starting shortly after birth, it is unknown whether this syndrome is accompanied by long-term impaired cognitive functioning. We therefore assessed cognitive functioning in male patients with IGSF1 deficiency.

Methods

Fifteen adult male patients with IGSF1 deficiency participated in neuropsychological assessment of executive functioning and memory, and completed validated questionnaires on health related quality of life (HRQoL), mood, and fatigue. Results were compared to data from previous studies by our department; 54 healthy controls (76 for the attention task) for the test battery and 191 healthy controls for the questionnaires.

Results

All patients had central hypothyroidism and twelve were treated with levothyroxine. Patients performed worse than controls in tasks that required attentional control (Trail Making Test, Letter-Digit Substitution Test, and Sustained Attention to Response Task) (all $P<0.001$). Memory was unaffected. In addition, patients reported more mental fatigue and reduction of activity (Multidimensional Fatigue Inventory) (both $P<0.01$), while HRQoL and mood reports were not different from controls. Age at start of replacement therapy and current thyroxine levels were not related to outcome.

Conclusions

Adult male patients with IGSF1 deficiency exhibit mild deficits in attentional control on formal testing. This finding was not related to the age at start of, or current levothyroxine treatment.

CONTEXT

Loss-of-function of the immunoglobulin superfamily member 1 (*IGSF1*) gene causes an X-linked endocrine syndrome in males, characterized by congenital central hypothyroidism, a delayed pubertal testosterone rise despite normal timing of testicular enlargement, adult macroorchidism, and in some cases prolactin or transient partial growth hormone (GH) deficiency (1;2).

Thyroid hormone plays a vital role in brain development and functioning, and an altered thyroid hormone state has been associated with abnormal cognitive functioning in children and adults (3). Although many aspects of endocrine dysfunction in IGSF1 deficiency have been studied, cognitive functioning was not assessed. In our experience, patients with IGSF1 deficiency often report attention problems in daily life, *e.g.* while studying for exams, playing sports like tennis, and even when having a conversation. These problems had been present for as long as they could remember and were often recognized by relatives and treating physicians. Indeed, five of the 32 male patients with IGSF1 deficiency currently known to our group, who are all younger than 25 years, had been diagnosed with attention deficit disorder (ADD), and two of them had been treated with psychostimulants (unpublished data). In addition to these observations, the penetrance of levothyroxine in target tissues in this genetic syndrome has been doubted (4).

The present study aimed to investigate cognitive functioning, specifically executive functioning and memory, in adult male patients with the X-linked IGSF1 deficiency syndrome. Patients were invited for neuropsychological examination, and completed validated questionnaires assessing health related quality of life (HRQoL), mood, and fatigue. Results were compared to healthy controls.

SUBJECTS AND METHODS

Design

Cognitive functioning was assessed in 15 patients with documented IGSF1 deficiency. The neuropsychological examination started at 9:00 AM, and patients were instructed not to drink coffee that morning. During the week following the examination, the patients completed several questionnaires at home assessing HRQoL, mood, and fatigue. Cognitive performance and questionnaire scores of patients were compared to control data from previous studies performed in our institution using similar protocols.

Patients and healthy controls

Inclusion criteria were Dutch male patients between 18 and 75 years old with documented pathogenic mutations in *IGSF1* (N = 18). Pathogenicity was based on the presence of central hypothyroidism, phenotype-genotype segregation, and *in silico* and *in vitro* pathogenicity of the mutated proteins, as previously described (1). Three patients chose not to participate because of long traveling distance, thus we included 15 patients with IGSF1 deficiency. Results were compared to data from healthy male controls between 18 and 75 years old: for the cognitive tasks from 54 subjects ((5;6) and unpublished), for the sustained attention to response task (SART) from 76 subjects ((7) and unpublished), and for the questionnaires from 191 subjects (8).

Methods

Cognition - executive functioning

The Trail Making Test involves scanning, visuomotor tracking, divided attention and cognitive flexibility. The patient has to connect digits with each other (Trail A), followed by connecting digits and letters (Trail B). The time that was used for each trail was noted, with more time used indicating lower performance (9).

The Stroop Color-Word Test was used to measure interference sensibility. One response (reading the word) should be inhibited in order to name the color of the ink, which leads to a delay in reaction time (10). The number of correct responses within 45 sec was counted.

The Letter-Digit Substitution Test measures visual scanning, cognitive flexibility, sustained attention, psychomotor speed and speed of information processing (11). The number of letters correctly substituted for digits within 60 sec was counted.

The FAS Test was used to assess verbal mental flexibility and fluency by testing the ability to produce as many words as possible with a specific starting letter (F, A, or S) (12). The number of correctly produced words within 60 sec was counted.

The Sustained Attention to Response Task (SART) is a test of attentional control assessing both attentional and inhibitory processes by addressing the capacity to attend to a situation or task in spite of distractibility, fatigue, or boredom (13). After a practice run, numbers from 1 through 9 appeared in random order and in different sizes in a white font on a black computer screen for 4 min and 20 sec, 225 times in all. Participants were asked to press a button in response to the appearance of each number, except when the number was a '3', which occurred 25 times. Participants were instructed to give equal importance to accuracy and speed in performing the task. The primary outcome was the total number of errors, consisting of errors of commission (*i.e.*, pressing after a '3') and errors of omission (*i.e.*, not pressing after any number but a '3'). A secondary outcome measure was reaction time (*i.e.*, the response time after the appearance of a number) and variability in reaction time. The test took place in solitude in a quiet room. The SART

was performed two times to correct for the learning effect, and only the second run was used (13). The time in between was spent on other tests (Rey Complex Figure, FAS, Letter-Digit Substitution Test, Stroop Color-Word Test).

Cognition - memory

The Wechsler Memory Scale (WMS) was used to assess learning, memory, and working memory using auditory and visual stimuli. Higher scores reflect better memory performance (14).

The Verbal Learning Test of Rey measures verbal memory and learning and consists of three trials in which fifteen words are presented visually. In addition, there is a fourth delayed reproduction. The number of correctly recalled words was counted for each trial. More produced words each trial, indicates a better learning capacity (15).

The Rey Complex Figure is a drawing and visual memory test and measures visual-motor organization by examining the ability to copy and remember a complex figure. Immediate recall and delayed recall are measured, and higher scores indicates better visual memory (16).

Questionnaires

The Short Form-36 (SF-36) assesses general well-being and functional status during the previous 30 days (17). The SF-36 contains nine dimensions, and scores are expressed on a 0–100 range. Because the HADS and the MFI-20 are more specific for mental health and fatigue, assessment of the dimensions 'vitality' and 'general mental health' from the SF-36 were not performed. Because the nine scales are scored separately from exclusive item-specific questions, the results of the scales presented in this study are not influenced by the two dimensions that were left out in this evaluation. Scores are expressed on a 0–100 scale, higher scores being associated with better quality of life.

The Hospital Anxiety and Depression Scale (HADS) assesses anxiety and depressive symptoms (18). Scores range from 0 to 21, with higher scores indicating more complaints.

The Multidimensional Fatigue Inventory (MFI-20) assesses fatigue in five dimensions (19). Dimension scores vary from 0 to 20, with higher scores reflecting greater fatigue.

Laboratory measurements

Free T_4, prolactin, cortisol, and testosterone levels were measured by electrochemoluminescent immunoassays (ECLIA), using a Modular E170 (Roche Diagnostics, Mannheim, Germany). The maximal inter-assay coefficient of variation (CV) for these hormones was 5.0%. Serum IGF-I concentrations in nmol/L were measured using an iSYS immunoanalyser of IDS GMBH in Frankfurt am Main, Germany. The IGF-I assay is standardized against the first international standard 02/254. The intra-assay CV at mean plasma levels of 6.5 and 14 nmol/L were between 62 and 6.8%, respectively. Serum GH was measured on an

Immulite 2000 XPi system (Siemens Healthcare Diagnostics, Deerfield, USA). Measured mU/L were converted to µg/L using a division factor of 2.6. Analytical variation at 5 and 25 mU/L were 5.2 and 4.5%, respectively.

Statistical analysis

Group differences were compared using the two-tailed independent Student's *t*-test or, in case the assumption of normality was not met (Shapiro-Wilk test), the Mann-Whitney U test. Categorical data were compared using the Chi square test or, when the expected cell count was less than 5, the Fisher's exact test. Linear regression models were used to correct for differences in age and education in the cognitive tasks, age and reaction time in the SART, and age in the questionnaires. To correct for multiple testing, differences were considered statistically significant at $P < 0.01$.

RESULTS

Clinical characteristics

We included fifteen adult male patients from ten unrelated families (Table 1). Median age was 25.4 years old (range 19.4 – 67.7 years). All were diagnosed with central hypothyroidism, and twelve of them were on stable levothyroxine replacement. Five patients started levothyroxine treatment shortly after birth, four in childhood, one in adolescence, and the remaining two at middle age. The remaining three patients were recently diagnosed in adulthood, did not show overt signs or symptoms of hypothyroidism, and were studied in the untreated condition. Eight patients were prolactin deficient, and GH deficiency was present in one patient who was treated with rhGH. One 25 year old patient was diagnosed with ADD in adolescence. He was treated with psychostimulants while studying for high school graduation, but stopped afterwards because of side effects. Brain MRI was previously performed in five patients, showing a frontoparietal hygroma in one patient (present at birth and treated with a ventriculoperitoneal shunt), but no abnormalities in the others. Exclusion of the patient with ADD and/or the patient with hygroma did not change the results.

All controls were healthy males between 18 and 75 years old. Mean age in controls was generally higher than that in patients, thus we corrected for age using regression analysis.

Cognition - executive functioning

Patients performed worse in several executive functioning tasks (Table 2). Compared to controls and corrected for age and education, patients were significantly slower in completing both trail A and B of the Trail Making Test (both $P \leq 0.001$), and substituted

Table 1. Clinical characteristics of IGSF1 deficient male patients

	Patients		Reference range
	mean ± SD or median (IQR)	range	
N	15		
Age (yr)	25.4 (22.9-56.7)	18.9 - 67.7	
BMI (kg/m^2)	28.0 ± 5.4	22.1-39.5	
Central hypothyroidism	15		
Free T_4 at diagnosis (%LL)	82.1 ± 10.2	65.8-95.4	>100%
TSH at diagnosis (mU/L)	2.300 ± 1.361	0.800-5.600	0.300-4.800
Levothyroxine replacement	12		
Growth hormone deficiency	1		
RhGH replacement	1		
Free T_4 (pmol/L)	14.3 ± 5.1	7.9-25.7	12.0-22.0
TSH (mU/L)	0.850 ± 0.671	<0.01-2.270	0.300-4.800
IGF-1 (SDS)	1.2 ± 1.5		*Age dependent (in-house)*
Basal GH (µg/L)	1.1 ± 1.5		0.0-2.8
Prolactin (µg/L)	6.3 ± 4.1		4.0-15.0
Testosterone (nmol/L)	15.7 ± 5.7		8.0-31.0
Cortisol (µmol/L)†	0.394 ± 0.169		0.100-0.600
Testicular volume (SDS)‡	3.9 ± 2.2		(39)

†Early morning cortisol level. ‡Ultrasonographic volume (π/6·length·height·width) of largest testis. SDS: standard deviation score. IQR: interquartile range. %LL: percentage of the lower limit of the age-specific reference range. All measurements were taken at the time of the study, except for free T_4 at diagnosis and TSH at diagnosis.

fewer words within one minute on the Letter-Digit Substitution Test (β = -7.8 (SE 2.2), P = 0.001).

Furthermore, patients performed markedly worse than controls on the SART (Table 3), as they made more errors of omission (P = 0.001) and commission (P < 0.001). Variability in reaction time was greater in patients than controls (P < 0.001). Since patients' reaction time tended to be quicker, possibly influencing the error rates (13), we corrected for reaction time as well as age, which did not change the results: patients made more than twice as many mistakes as controls (11.8 more mistakes, 95% CI 8.4-15.2). Results were unavailable in one patient due to failure of the device to automatically store results. Neither free T_4 levels, nor age of start of replacement therapy correlated with executive functioning (corrected for age and education).

Patients' performance in the Verbal Fluency Test and Stroop Color-Word test were not different from controls.

Table 2. Cognitive tasks

	Patients	Controls	*P*	*β** (SE)	*P*
n	15	54			
Age (yr)	36.1 ± 18.8	55.5 ± 11.8	**.001**		
Male gender	15	54	1.000		
Education level†					
High	8 (53%)	18 (33%)			
Intermediate	6 (40%)	19 (35%)	0.138		
Low	1 (7%)	17 (32%)			
Executive Functioning					
Verbal Fluency Test, no. of correct	35.3 ± 7.8	34.6 ± 13.4	.839	-1.2 (4.3)	.774
Trail Making Test					
Trail A, time (min)	0.46 ± 0.13	0.40 ± 0.21	.018	0.2 (0.1)	**.001**
Trail A, no. of errors	0.4 ± 0.5	0.2 ± 0.4	.083	0.2 (0.1)	.245
Trail B, time (min)	1.15 ± 0.51	1.11 ± 0.53	.771	0.5 (0.1)	**<.001**
Trail B, no. of errors	0.4 ± 0.5	0.8 ± 1.2	.418	0.0 (0.3)	.932
Letter-Digit Substitution Test					
No. of correct	29.9 ± 6.6	32.6 ± 7.4	.218	-7.8 (2.2)	**.001**
No. of errors	0.1 ± 0.5	0.1 ± 0.2	.829	0.1 (0.1)	.473
Stroop Color-Word Test, interference total	44.7 ± 10.2	40.1 ± 9.9	.033	-3.8 (2.8)	.190
Memory					
Wechsler Memory Scale					
MQ	114.6 ± 15.8	116.3 ± 14.4	.700	1.3 (4.7)	.778
Information	6.0 ± 0.0	5.9 ± 0.2	.350	0.1 (0.1)	.441
Orientation	5.0 ± 0.0	5.0 ± 0.0	1.000	0.0 (0.0)	1.000
Concentration	7.7 ± 2.1	7.3 ± 1.8	.193	-0.5 (0.6)	.376
Digit span	12.1 ± 3.8	9.9 ± 1.6	.038	1.5 (0.8)	.062
Logical memory	7.5 ± 2.8	7.4 ± 2.7	.967	-0.7 (0.9)	.450
Visual memory	12.2 ± 1.9	9.2 ± 3.5	**.001**	0.9 (1.0)	.359
Associative learning	16.4 ± 3.2	16.6 ± 2.7	.971	-1.8 (0.9)	.049
Verbal Learning Test of Rey					
Imprinting, total no.	5.8 ± 2.2	5.3 ± 1.8	.331	-0.4 (0.6)	.523
Immediate, total no.	8.9 ± 2.2	8.6 ± 2.1	.644	-0.9 (0.7)	.181
Immediate 2, total no.	10.5 ± 2.2	9.8 ± 2.2	.286	-0.7 (0.7)	.364
Delayed, total no.	8.3 ± 2.8	8.0 ± 2.8	.762	-1.2 (0.9)	.200
Rey Complex Figure Test					
Immediate	24.6 ± 5.5	20.9 ± 6.6	.046	-0.1 (2.0)	.964
Delayed	23.9 ± 5.6	20.9 ± 6.2	.098	-0.8 (1.9)	.684

Data represent number (percentage) or mean ± SD, unless specified otherwise. *Linear regression model assessing the effect of disease, corrected for age and education. †Low: primary education (elementary school) and lower secondary education (preparatory secondary education); Intermediate: higher secondary education (higher general continued education, pre-university secondary education) and post-secondary education (intermediate vocational education); High: tertiary education (higher professional education, university). Statistically significant differences ($P < 0.01$) are marked in *bold*.

Table 3. Sustained attention to response task (executive functioning)

	Patients	Controls	*P* value	*β** (SE)	*P* value
n	14[†]	76			
Age	36.8 ± 19.3	45.6 ± 12.8	.072		
Male gender	15	76	1.000		
Errors of omission	6.0 ± 6.6	0.9 ± 1.8	**.001**	4.7 (0.9)	**<.001**
Errors of commission	18.8 ± 3.5	10.2 ± 4.8	**<.001**	7.0 (1.2)	**<.001**
Total no. of errors	24.8 ± 9.2	11.1 ± 5.9	**<.001**	11.8 (1.7)	**<.001**
Mean RT (ms)	250.8 ± 45.2	277.3 ± 42.8	.082		
RT variability (ms)	138.2 ± 69.0	69.1 ± 27.1	**<.001**		

Data represent mean ± SD or beta coefficient (SE). *Linear regression model assessing the effect of disease, corrected for age and reaction time. [†]Results from one patient were unavailable. RT: reaction time. Statistically significant differences ($P < 0.01$) are marked in *bold*.

Cognition - memory

Memory function was normal in patients, as they performed similar to controls in the WMS, the Verbal Learning Test of Rey, and the Rey Complex Figure Test (Table 2). Initial differences between patients and controls in the WMS subscale visual memory did not persist after correction for age and education.

Questionnaires

Patients reported more mental fatigue and a reduction in activity in the MFI-20 (both $P < 0.01$, corrected for age) (Table 4). No significant differences were observed in patients' responses in the SF-36 or HADS. Neither free T_4 levels nor age at start of replacement therapy were associated with outcome after correcting for age.

Table 4. Questionnaires on health related quality of life, mood, and fatigue

	Patients	Controls	*P* value	*β** (SE)	*P* value
n	15	191			
Age	36.1 ± 19.0	53.4 ± 12.6	**.001**		
Male gender	15	191	1.000		
SF-36					
Physical functioning	91.7 ± 20.2	91.7 ± 12.8	.290	-6.2 (3.6)	.084
Social functioning	90.0 ± 17.2	93.7 ± 13.4	.221	-6.1 (3.9)	.118
Role physical problem	81.7 ± 38.3	90.5 ± 22.8	.787	-11.4 (6.8)	.098
Role emotional problem	82.2 ± 33.0	91.7 ± 22.4	.206	-9.1 (6.6)	.170
Pain	89.6 ± 22.7	89.6 ± 14.9	.958	-6.0 (4.4)	.164
General health perception	76.3 ± 21.3	73.9 ± 15.8	.238	-3.4 (4.5)	.442
Health change	55.0 ± 19.4	53.4 ± 16.1	.727	-0.7 (4.7)	.881

Table 4. (continued)

	Patients	Controls	*P* value	*β** (SE)	*P* value
HADS					
Anxiety	4.4 ± 3.6	3.2 ± 2.5	.285	0.9 (0.7)	.229
Depression	2.8 ± 3.4	2.6 ± 2.7	.839	0.9 (0.8)	.244
Total	7.2 ± 6.8	5.8 ± 4.3	.787	1.8 (1.3)	.170
MFI-20					
General fatigue	9.4 ± 4.3	7.4 ± 3.5	.054	1.7 (1.0)	.086
Physical fatigue	7.8 ± 4.5	7.2 ± 3.3	.880	1.3 (1.0)	.172
Reduction in activity	9.3 ± 4.3	7.0 ± 3.1	.019	2.7 (0.9)	**.003**
Reduction in motivation	7.7 ± 3.6	6.9 ± 3.1	.394	1.0 (0.9)	.255
Mental fatigue	12.0 ± 5.2	7.1 ± 3.2	**<.001**	4.8 (1.0)	**<.001**

Data represent mean ± SD or beta coefficient (SE). *Linear regression model assessing the effect of disease, corrected for age. Statistically significant differences ($P < 0.01$) are marked in *bold*.

DISCUSSION

The present study demonstrates that patients with IGSF1 deficiency have mild deficits in attentional control with preserved memory function. Furthermore, patients reported more mental fatigue and a reduction in activity, while HRQoL and mood estimates were not affected.

Adult patients with IGSF1 deficiency performed worse than controls in tests that primarily assess attentional processes (the Trail Making Test, Letter-Digit Substitution Test, and SART). The Trail Making and Letter-Digit Substitution Test are paper-and-pencil speed tests that require perceptual-motor speed or focussed attention in order to scan and select target information from an array rapidly and efficiently, and make a skilled manual response quickly (also known as "focus-execute" attention (20)). The SART was designed to test sustained attention, i.e. the capacity to maintain focus and alertness over time (also known as "vigilance"(20)). However, the SART also requires focussed attention and inhibition (withholding a pre-potent response (20), *e.g.* commission errors), and the Trail Making and Letter-Digit Substitution Test also require sustained attention (20), since all of these attentional processes are highly interdependent. We therefore chose to classify the observed alterations using the overarching construct of top-town control or coordination of action within the network of structures responsible for complex goal-oriented behaviour known as 'attention control' (21).

The Stroop Color-Word Test also requires attentional control (20). Although patients performed slightly worse than controls in this test, differences were not statistically significant. This inconsistency with the Trail Making and Letter-Digit Substitution Test

might be explained by the required response being verbal rather than manual. Mental flexibility (Verbal Fluency Test) was normal.

Reductions in attentional control were also experienced subjectively by patients, as they reported more problems in the MFI-20 subscales mental fatigue (*i.e.* 'When I am doing something, I can keep my thoughts on it / My thoughts easily wander' and 'I can concentrate well / It takes a lot of effort to concentrate on things') and reduction in activity (*i.e.* 'I feel very active' and 'I think I do a lot in a day / I think I do very little in a day / I get little done'). Since patients reported no disturbances of general and physical fatigue in the MFI-20, nor of physical functioning in the SF-36, the observations are unlikely explained by physical tiredness. These complaints may be a consequence of the deficits in attentional control, or share a common aetiology with these deficits.

Nevertheless, the clinical significance of the observations for patients is hard to assess. Since IGSF1 deficiency is congenital, functioning cannot be compared to a pre-disease state. Furthermore, attention was sufficient to perform well in tasks of memory in the Wechsler Memory Scale, the Verbal Learning Test of Rey, and the Rey Complex Figure Test, as well as mental flexibility in the Verbal Fluency Test. Also, while some reported problems with concentrating during consultations, most patients did not consult a professional for complaints of attentional control, educational level was normal and matched current profession, and differences with the controls' mean were often less than two standard deviations scores (Trail Making Test: 1.0±0.3 SDS, Letter-Digit Substitution Test: 1.1±0.3 SDS, SART errors of omission: 2.6±0.5 SDS and commission: 1.5±0.3 SDS, MFI-20 reduction in activity: 0.9±0.3 SDS and mental fatigue: 1.5±0.3 SDS). We therefore consider the symptoms to be mild.

Our results are in good accordance with several studies in children with (early treated) congenital hypothyroidism that report disturbances of especially the attention components focussed attention, inhibition, and sustained attention (22-24), especially in those with prematurity or the lowest plasma or serum T_4 concentrations in the neonatal period (25-27). Therefore, the difficulties with attentional control in patients with IGSF1 deficiency might be related to inadequate (prenatal) T_4 concentrations during critical periods of brain maturation, rather than to abnormal T_4 concentrations in adulthood. This is supported by the absence of a correlation between executive functioning and either free T_4 concentrations or age of start of replacement therapy in the IGSF1 deficient patients. Moreover, adults with acquired primary hypothyroidism usually report symptoms of anxiety and depression (which were not present in patients with IGSF1 deficiency), and rarely present with problems in the cognitive domain (28), although some studies reported impaired (sustained) attention in patients treated for autoimmune hypothyroidism while not in other causes of acquired primary hypothyroidism (29;30). On the other hand, direct effects of IGSF1 on adult executive functioning cannot be excluded, as IGSF1 is expressed in the adult rat cerebral cortex, striatum, subfornical

organ, amygdala, and in glial cells of the hypothalamus (31). Although IGSF1's function in these brain regions is still unknown, other members of the Ig superfamily are involved in the development and maintenance of various parts of the central nervous system (32;33).

Of special interest are patients with generalized resistance to thyroid hormone (GRTH), a disorder caused by mutations in the thyroid hormone receptor beta (THRB) gene, characterized by reduced responsiveness of peripheral and pituitary tissues to thyroid hormone. Forty-eight to 73% of these patients have been found to show attention deficit-hyperactivity disorder (34). Several studies confirmed the relation between this defect and especially sustained attention and ADD, which might be related to higher glucose metabolism in the right parietal cortex and anterior cingulate gyrus (35). Treatment with liothyronine sodium, and not levothyroxine, improved these complaints (36). Moreover, TRB knock-out mice show disturbances of sustained attention and are used as a model for ADD (37). In our adult patient group, we observed no relation between outcome and T_4 concentrations at the time of evaluation or the age of start replacement therapy, raising the question whether the current treatment in these patients is sufficient. The pathophysiology of IGSF1 deficiency is still unresolved, but given the similarities with GRTH it would be interesting to treat these patients with liothyronine and re-evaluate cognitive functioning.

Besides congenital central hypothyroidism, a number of patients with IGSF1 deficiency exhibit persistent prolactin deficiency or transient partial GH deficiency in childhood. There are no reports of associations between these conditions and vigilance. We also previously reported a frontoparietal hygroma, a small pituitary stalk lesion, and hypoplasia of the corpus callosum in three of eleven brain MRI studies in IGSF1 deficient patients (1). Associations between callosal efficiency and vigilance have been reported (38). However, since the integrity of the corpus callosum was normal in all other MRI's, callosal inefficiency is unlikely to explain the profound disturbances observed in patients with IGSF1 deficiency.

An obvious limitation of this study is its small group size, which is inherent to the low prevalence of IGSF1 deficiency. A second limitation is that we did not include a matched control group. However, we were able to select large groups of controls that were studied with similar protocols in our institution, and corrected for differences in age or education level. We contend that the observations are both clear and informative.

In conclusion, this first study on cognitive functioning of adult male patients with the X-linked IGSF1 deficiency syndrome showed that these patients exhibit mild deficits in attentional control with preserved memory function. Furthermore, patients reported more mental fatigue and reduced activity. These results resemble findings in other congenital disorders involving thyroid hormone, especially GRTH, but were not related to current treatment with levothyroxine or the age at which replacement therapy was

initiated. Future research in (juvenile) patients and animal models is needed to further elucidate whether these deficits are caused by irreversible damage from intra-uterine hypothyroxinemia, or whether they are related to decreased sensitivity to treatment with levothyroxine. Either way, physician awareness of the presence of these deficits in patients with IGSF1 deficiency may be helpful during consultations. If necessary, neuropsychological interventions or treatment with psychostimulants may be considered.

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