FONDAZIONE "ISTITUTO NEUROLOGICO NAZIONALE C. MONDINO"
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

UNIVERSITA' DEGLI STUDI DI PAVIA

GLUT1 DS
The cognitive aspects

Valentina De Giorgis

The State-and-Region Agreement asks for a declaration by Moderators, Speakers, Teachers and Tutors about the frankness of the financing sources and about their relationships with people with commercial interests within the last two years, only if there could be a conflict of interests.
The documents must be available at the Provider offices for at least 5 years.

Conflict of Interests Declaration

Undersigned _____ DE GIORGIS VALENTINA_____ as:

□ scientific responsible □ moderator □ teacher x speaker □ tutor

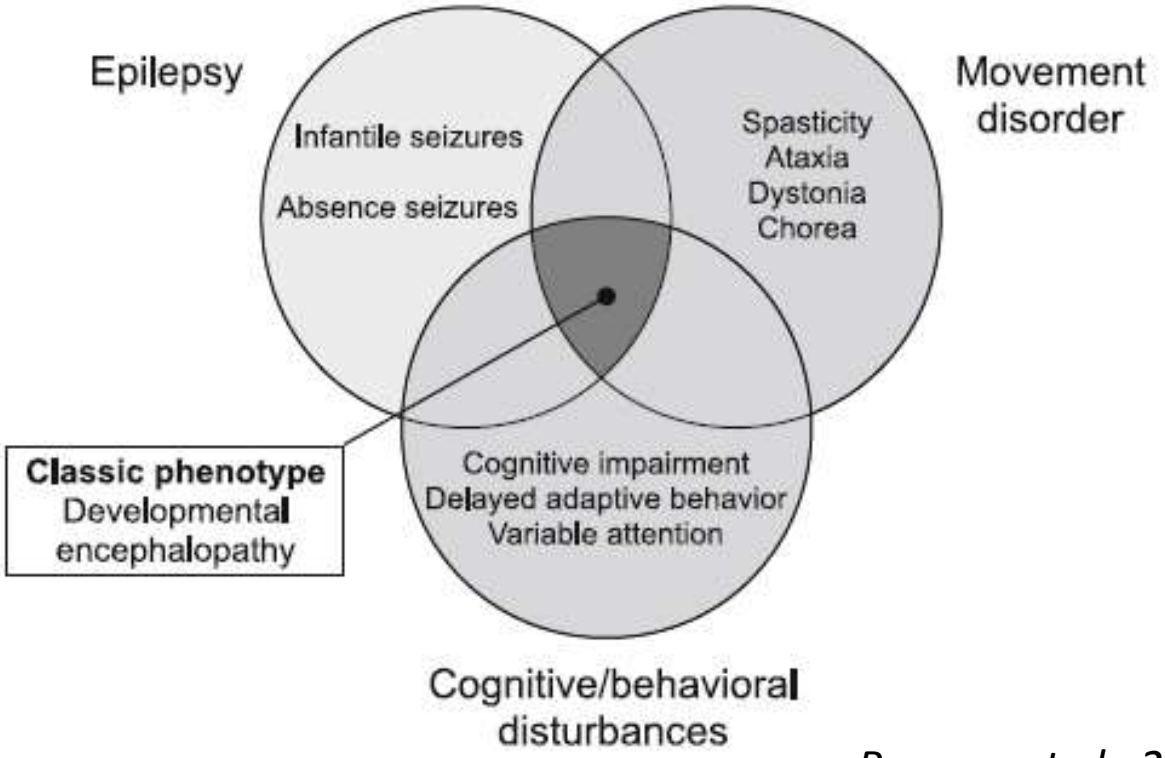
of the event "**1st European Conference on Glut1 Deficiency**"
Milan - Italy, 7th-8th October 2016

Based on Art.. 3.3 about the Conflict of Interests, page 18,19 of the State-and-Region Agreement dated 19 April 2012, managed by **Biomedia n. 148**

Declares

that in the last two years DIDN'T have any relationships about comercial financings with people having conflict of interests in the health field

GLUT1 deficiency sindrome



Pearson et al., 2013

Paper	Total N	Data available	Intellectual disability (before KD)				Other neuropsich	KD cognitive and behavioural improvement
			n° (%) ID patients	severe	moderate	mild		Pre/post
Klepper et al. 2005	15	15	15 (100%)					Parents reported an increase of alertness and activity on diet
Coman et al. 2006	8	8	8 (100%)		1	1	6 developmental dealy	1 patient more alert and interactive
Rotstein et al. 2009	1	1	1(100%)			1		
Suls et al. 2009	4	4	3 (75%)		1	1 mild, 1 borderline (78)		
Cigdem et al. 2010	13	13	11 (85%)		1	5 mild, 5 borderline		
Leen et al. 2010	57	54	53 (98%)	8	21	24		21/44 subjective improvement of cognitive function, alertness and behaviour
Ito et al. 2011	6	6	6 (100%)	4	1	1		MAD P1: 65/67; P2: 33/41; P3: 30/35; P4: 48/50 Improvement in vigilance level and motivation (6/6), comprehension (5/6), concentration (4/6)
Koy et al. 2011	1	1	1 (/100%)			1	Visuomotor skills and spatial sense developmental delay	
Ramm-Pettersen et al. 2013	10	9	6 (67%)		2	2 mild, 1 learining disability	1 psychomotor retardation, no eye contact	P3: psychomotor retardation, no eye contact/ major improvement, more alert P4: moderately retarded/ slightly retarded P5: slightly retarded/learining disability
Leen et al. 2014	7	7	7 (100%)	1	2	4		6 pz, + effect on cognition
Ragona et al. 2014	1	1	1 (100%)			Borderline IQ	ADHD, visuospatial and verbal memory	
Ramm-Pattersen et al. 2014	6	6						KD P1:; P2: baily SS5/WPPSI-III 102; P3: WPPSI-III 42/63; P4: WISC-IV 49/54 MAD P5: ; P6: WASIm53/53 Improvement in visuomotor precision, sensorimotor speed, expressive and receptive language
Tzadok et al. 2014	17	8	4 (50%)			2 mild, 2 learning disability	2 ADHD 1 behavioral problems	Clinical impression of cognitive improvement (2 pz no ID)
Almuqbil et al. 2015	1	1	1 (100%)		1			
Alter et al., 2015	13	13	13 (100%)	4	3	6	13 exceptional empathy	7 KD 7/7 no improvement in cognitive functions
De Giorgis et al. 2015	22	22	21 (95,5%)		5	6	10 borderline	13 KD 5/13 (37%) improvement in cognitive function, alertness and activity P n12: 79/89
Ito et al. 2015	57	33	33 (100%)	12	9	12 borderline-mild	24% learning disabilities and ADHD	
Hully et al., 2015	58	24	92%	5	12	5		68% improv cognitive and behaviour
Larsen et al. 2015	6	6	4 (67%)		4	1		
Total	**303**	**232**	**189 (81,5%)**	**34 (18%)**	**63 (33 %)**	**92 (49%)**		

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Does ketogenic diet improve cognitive function in patients with GLUT1-DS? A 6- to 17-month follow-up study

Anette Ramm-Pettersen [a,*], Kirsten Engberg Stabell [a], Karl O. Nakken [a], Kaja Kristine Selmer [b,c]

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[b] Department of Medical Genetics, Oslo University Hospital and University of Oslo, Norway
[c] National Centre for Rare Epilepsy-related Disorders, Oslo University Hospital, Norway

Table 2
Neuropsychological test results before and 6–17 months after institution of KD or MAD.

	Patient 1 (Pre/postdata)	Patient 2 (Pre/postdata)	Patient 3 (Pre/postdata)	Patient 4 (Pre/postdata)	Patient 5 (Pre/postdata)	Patient 6 (Pre/postdata)
Age at testing	1 y 8 m/2 y 2 m	2 y 3 m/3 y 8 m	4 y 7 m/5 y 9 m	10 y 4 m/11 y 4 m	34 y 8 m/35 y 6 m	29 y 10 m/30 y 8 m
Interval diet start to retest	6 m	17 m	14 m	12 m	10 m	10 m
General cognitive index	Bayley-III SS 8/8	Bayley-III SS 5/WPPSI-III **FSIQ: 102**	WPPSI-III FSIQ 42/**63**	WISC-IV FSIQ 49/54	WPPSI-III AE: 3 y 5 m–5 y 7 m/ AE: 3 y 5 m–5 y 7 m	WASI FSIQ 53/53
Verbal IQ	NSO	NSO/111	WPPSI-III 57/61	WISC-IV 50/54	NSO	WASI 55/55
Performance IQ	NSO	NSO/92	WPPSI-III 45/**63**	WISC-IV 47/**62**	NSO/ AE: 3 y 4 m–4 y 7 m	WASI 57/58
Language, expressive	Bayley-III SS 6/7	Bayley-III SS 5/ WPPSI-III SS 6	WPPSI-III Naming (SS) 5/5	WISC-IV Vocabulary (SS) 2/3	WPPSI-III Naming (RS) 17/**21** AE: 4.1/**5.1**	NEPSY Fluency (RS) 5/**13** AE: <3/**4.0**
Language, receptive	Bayley-III SS 8/**10**	Bayley-III SS 7/ WPPSI-III **SS 16**	WPPSI-III Vocabulary SS 6/8	Token Test (RS) 23/21	WPPSI-III Vocabulary 28/28 (RS) AE: 5 y 7 m/5 y 7 m	NEPSY sentences 11/12 (RS)
Verbal learning Delayed recall Recognition Narrative Memory	NA	NA	NA	CAVLT-II (StS) 88/68 (RS) 17/**25** (RS) 8/**14**	NSO	10 words (RS) 0/**7** (RS) NSO/**9** (RS) 8/**12**
Attention Working Memory Processing Speed	NA	NA/NSO	NEPSY NSO/RS **32** (>75 p)	WISC-IV (SS) 70/60 (SS) 51/54	NEPSY (RS) 286/**159**	NEPSY (RS) 172/**115**
Visuomotor Precision	NA	NA/NSO	NA	VMI (T-sc.) <20/**31**	NEPSY (RS) 92/**76**	NEPSY (RS) 153/**129**
Sensorimotor speed	Bayley-III (SS) Fine: 8/9 Gross: 3/**5**	Bayley-III (SS) Fine: 4/7 Gross: 6/**9**	NEPSY pegs (RS) RH: 168/**83** LH: 280/**99**	Pegboard (RS) RH: 201/**167** LH: 249/**203**	NEPSY pegs (RS) (RH + LH) 284/323	Pegboard (RS) RH: 450/**195** LH: 225/240
Hand dominance		Right	Right	Ambidxt.	Right	Left
Caretakers' report improvements						
Alertness	+	(+)	++	++	++	++
Language	+	(+)	+	+	++	+
Social engagement	+	(+)	+	+	+	+
Articulation	+	+	+	+	+	+
Physical endurance	+	Intact	+	++	++	++

Symbols: + = improved; ++ = much improved. Abbreviations: AE = age equivalent (in months); Ambidxt. = ambidextrous, i.e., equal use of both hands; FSIQ = Full-scale IQ (M = 100, SD = 15); LH = left hand; m = months; NA = not applicable; NSO = no score obtainable; p = percentile; RH = right hand; RS = raw score; SS = scaled score (M = 10, SD = 3); StS = standard score (M = 100, SD = 15); T-sc. = T-score (M = 50, SD = 10); y = years.
Note: For raw scores on Token Test, NEPSY Visuomotor Precision, Visual Attention, and 10 pegs and on Pegboard: the lower the score, the better the performance. Test results marked in bold type are considered to indicate positive effects of the diet.

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The main findings were:

- ✓ a considerable improvement in several aspects of neuropsychological functioning after 6–17 months of dietary treatment
- ✓ the greatest progress was seen in the youngest children
- ✓ also adults with GLUT1-DS may profit from dietary treatment by improving alertness, setting the stage for enhanced learning capacity, as well as physical endurance and quality of life.
- ✓ tests on visuomotor precision and sensorimotor speed showed the most frequent and marked improvements
- ✓ early diagnosis and dietary treatment are important in order to prevent developmental delay

Long-Term Clinical Course of Glut1 Deficiency Syndrome

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Aliza S. Alter, MD[1], Kristin Engelstad, MS[1], Veronica J. Hinton, PhD[1,2], Jacqueline Montes, PT, EdD[1], Toni S. Pearson, MD[1], Cigdem I. Akman, MD[1], and Darryl C. De Vivo, MD[1]

Long term follow-up: 14.2 years
N: 13 patients
Mean age at start diet: 4.2 y
Mean duration of KD: 8.8 y
Patient still on diet: 7

Table 1. Entry Data Characteristics of 13 Study Subjects.

Participant	Age (y) at initial visit	Age (y) at follow-up	Duration (y) of follow-up	Gender	Mutation type	Mutation	Disease severity category	3-OMG uptake (%)	Initial CSF glucose (mg/dL)	Initial CSF-blood glucose ratio	Age (y) at start of KD	Duration (y) of KD	Still on KD?
1	0.6	23.7	23.1	M	Microdeletion	Null allele	Moderate	35	34	0.33	0.7	12.3	N
2	2.3	24.0	21.7	F	Nonsense	Y449X	Mild	43	25	0.27	2.3	21.8	Y
3	4.2	27.8	23.6	M	Missense	S66F	Mild	45	34	0.35	7	6	N
4	7.3	20.8	13.5	M	Splice site	972+1G>T	Moderate	49	27	0.32	3	8	N
5	0.1	15.3	15.2	M	Splice site	678T>G, 679G>A, 679+1del TACGGGCATG	Minimal	56	32	0.33	0.2	15.1	Y
6	8.8	22.7	13.9	M	Missense	R333W	Mild	43	34	0.4	8.4	0.3	N
7	16.8	28.0	11.2	M	Missense	R126H	Moderate	63	38	0.39	N/A	0	N
8	31.6	43.3	11.7	F	Missense	R126C	Minimal	54	**	**	N/A	0	N
9	8.2	18.8	10.6	M	Nonsense	Q397X	Severe	50	30	0.37	8.2	10.6	Y
10	5.5	15.5	10	M	Deletion	1216_1220 delGTTGC	Severe	50	35	**	3	12.5	Y
11	0.3	9.8	9.5	M	Missense	G130S	Minimal	66	30	0.35	0.3	9.6	Y
12	4.7	13.6	8.9	F	Deletion	385-387 delATC	Severe	53	32	0.36	4.4	9.2	Y
13	6.2	17.8	11.6	M	Missense	R153C	Severe	51	36	0.41	9	8.8	Y
Mean	7.4	21.6	14.2					51	32.3	0.35	4.2	8.8	
SD	8.5	8.5	5.2					8	3.7	0.04	3.4	6.3	

Abbreviations: CSF, cerebrospinal fluid; KD, ketogenic diet; SD, standard deviation; 3-OMG, 3-*O*-methyl-D-glucose.

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Table 3. Mean Performance on Individual Cognitive Tests at Baseline and Follow-Up.[a]

Test measure	Baseline	Follow-up	Overall difference	Paired *t* statistic	*P* value
Peabody Picture Vocabulary Test	78.92 (22.15)	75.17 (32.48)	3.75 ([illegible].45)	0.67	.52
Ravens Coloured Matrices	78.27 (20.07)	83.64 (12.31)	−5.36 ([illegible].03)	0.99	.35
Beery Test of Visual Motor Integration	67.92 (14.89)	61.42 (12.07)	6.5 ([illegible].49)	3.01	.01*

[a]Data are presented as Mean (Standard Deviation). n = 12.

Table 4. Mean Performance on Adaptive Behavior Domains at Baseline and Follow-Up.[a]

Vineland scales of adaptive behavior domain	Baseline	Follow-up	Overall difference	Paired *t* statistic	*P* value
Communication	65.90 (28.83)	65.60 (28.43)	0.30	0.04	.97
Daily living	61.90 (30.09)	63.80 (22.23)	−1.90	0.49	.63
Socialization	80.50 (23.90)	69.50 (25.12)	11.00 (25.49)	1.36	.21

[a]Data are presented as Mean (Standard Deviation). n = 10.

- Certain brain regions may be particularly susceptible to injury from neuroglypenia (thalamic injury)
- Neurologic, cognitive and adaptative skills remain stable over time
- Decline of visual-motor integration
- Early introduction o f KD is the most effective intervention though it may not affect all symptoms

Refractory Absence Epilepsy and Glut1 Deficiency Syndrome: A New Case Report and Literature Review

Francesca Ragona[1] Sara Matricardi[1,2] Barbara Castellotti[3] Mara Patrini[1] Elena Freri[1] Simona Binelli[4] Tiziana Granata[1]

Follow-up 6 years
Female
Atypical Absence epilepsy: seizures worsen before meals

6 years: TIQ 106 VIQ 104 PIQ 105 (WISC-III)
8 years: TIQ 95 VIQ 99 PIQ 92 (WISC-III)
12 years: TIQ 84 VIQ 88 PIQ 83 (WISC-III)

- Attention deficit
- Impairment in executive functions
- Visuospatial and verbal memory

GLUT1 DS population: 41 patients

pt	gender	age (y)	ratio	HC (p)	IQ	Spasticity	seizure	seizure onset (m)	seizure type	DR	EEG	MD	MD type	MD subtype	MD onset (m)	other	KD response
1	F	20	0.33	>50°	<45	y	y	6	ABS GTC MS	y	SB G	y	C	a	12	Ds Pr W Mi	EEG E MD W
2	F	19	0.33	>50°	<45	y	y	3	FS, ABS, GTC MS	y	SB G F	y	C	a c	8	Ds	EEG E MD
3	F	20	0.38	25-50°	<45	y	y	4	ABS FS MS	y	SB G F	y	C	a	18	Ds Pr W Mi	EEG E MD W
4	F	14	0.44	<25°	53	y	y	18	DS	y	SB F	y	C	a	20	Ds	EEG E MD
5	F	6	0.54	<25°	76	n	y	11	GTC ABS	n	SB G	y	PED	d	36	W	E MD W
6	F	10	0.34	<25°	40	n	y	30	MAS, DS, ABS	y	SB G F	y	PED	d	72	Ds W	E MD W*
7	F	13	NA	<25°	84	n	y	11	ABS	y	SB G	y	N	N	NA	M	NA
8	F	17	0.41	>50°	62	y	y	72	ABS	n	G	y	PND	a m	72	Mi	E EEG
9	M	17	0.51	<25°	57	n	y	72	CFS	n	F	y	PED	d	168	Ds	E MD
10	M	11	0.51	<25°	82	n	y	30	CFS	n	F	y	PED	c d	96	M	MD
1 1	F	2	0.37	25-50°	50	n	y	9	MAS	NA	SB G	n	/	/	/	/	E EEG
12	F	5	0.39	<25°	104	n	y	NA	DS, GTC, ABS	n	SB G F	y	C	a	16	/	EEG E MD
13	M	10	0.47	25-50°	75	n	y	72	DS	y	SB F	y	PED	c	60	W Mi	EEG E MD IQ
14	F	43	NA	> 50°	78	n	y	72	ABS	n	SB	n	/	/	/	Mi Pr	NA
15	M	35	NA	> 50°	60	n	y	8	DS	n	N	y	PED	d/ c	240	M	NA
16	F	57	NA	> 50°	74	n	y	60	ABS	n	N	n	/	/	/	M	NA
17	M	28	NA	> 50°	85	n	y	48	ABS	n	N	y	PED	d/ c	60	/	NA
18	M	49	NA	>50°	75	n	n	/	/	/	N	y	PED PND	d	144	W	NA
19	F	10	0.38	< 25°	66	n	n	/	/	/	N	y	PED	d/c	36	/	MD
20	F	29	0.44	> 50°	55	n	y	12	ABS, GTC	n	SB G	y	PED	/	NA	/	NA
21	F	24	NA	> 50°	76	n	y	72	ABS	n	G	n	/	/	/	/	NA
22	F	27	NA	> 50°	72	n	y	74	ABS	n	G	y	PED	/	NA	/	NA
23	F	19	0.50	>50	80	n	y	36	ABS	n	SB G	y	PED	d	7	O / M	NA
24	F	7	NA	>50	93	n	y	NA	ABS	n	SB G	n	/	/	/	/	NA
25	M	39	NA	>50	95	n	y	NA	ABS	n	SB G	y	PED	d	NA	/	NA
26	M	15	0.44	>50	44	n	n	/	/	/	/	y	PED	d / m	15	O / M /Ds	MD
27	F	17	0.56	>50	55	n	y	36	GTC, FS	y	SB G F	y	PED	d	174	M	MD
28	F	12	0.38	>50	75	n	y	36	ABS, MAS	y	SB G	y	PED	d	36	Pr	E EEG MD
29	F	7	0,36	>50	55	n	y	6	MS	y	SB G	n	/	/	/	O	E EEG
30	F	13			79	n	y		ABS	n		y	PED	d	120		NA
31	M	19	0,39	<10°	50	n	y	17	MAS	n		n	/	/	/	O	NA
32	M	10	0,5	>50	99	n	n	/	/	/	N	y	PED	d	60	W	MD
33	F	43	NA	NA	NA	n	n	/	/	/	NA	y	PED	D	?		NA
34	F	12	NA	>50	NA												
35	F	11	0,74	>50	40	n	y	12	MAS ABS	n	SB GF	n	/	/	/		E EEG
36	M	52	NA	>50	N	n	n	/	/	/	/	n	/	/	/	/	NA
37	M	23	NA	>50	NA	n	n	/	/	/	/	n	/	/	/	Mi	NA
38	M	11	0,41	>50	NA	y	y	y	FS	n	SB F	y	/	m	/	/	NA
39	M	11	NA	>50	NA	y	y	y	FS	n	SB F	y	/	m	/	/	NA
40	M	0,5	NA	>50	NA	n	/	/	/	/	/	n	/	/	/	/	NA
41	M	47	NA	<50	NA	n	y	1	ME	n	SG G	n	/	/	/	O	NA

25 patients (7 males and 18 females)
Mean age: 13.25 years (3.7 – 40)

Pt	mutation	type	ratio	KD onset	EEG efficacy	Epilepsy efficacy	MD efficacy	age at T0	TIQ	VIQ	PIQ
1	R153C	missense	0.39	52	1	1	1	65	99	104	98
2	R458W	missense	0.47	129	1	1	1	120	79	67	96
3	R126C	missense	0,34	119	0	1	1	118	43	54	45
4	R223W	missense	0,51	146	0	0	1	123	77	81	77
5	P36R	missense	0,44	161	1	1	1	161	48	59	48
6	V165I	missense	0.38	84	0	0	1	102	66	63	76
7	p.N34S	missense	0,35	84	1	1	0	59	59	76	71
8	Q283X	non sense	0.33	235	1	1	1	235	45	45	45
9	c 1457delG_1delG SPL	spice site	0.54	96	0	1	1	133	79	94	89
10	W48X	non sense	0.33	221	1	1	1	221	50	65	45
11	R126C	missense	0, 38	245	1	1	1	245	51	59	54
12	c.457C>T	missense	0.56	189	0	0	1	144	63	75	59
13	R400H	missense	0,44	180	0	0	1	170	44	55	45
14	p.Arg 400 cys	missense	0,38	112	1	1	1	131	52	56	58
15	c.884C>T	missense	0,42	169	1	1	1	163	84	118	74
16	p.Va1166del	deletion	0,5	233	1	1	1	228	93	95	92
17	p.Leu124Trpfsx12	frame shift	0,36	80	1	1	1	87	46	53	51
18	c.1551C>T	missense	0.51	223	0	1	1	153	57	50	65
19	g.33056 A>G	missense	0,5	118	/	/	1	118	99	114	87
20	c.26C>T	missense	0,52	122	1	1	/	107	91	101	83
21	g.33459-10delAG	deletion	0,37	22	1	1	/	45	74	83	81
22	c.1192G>A	missense	0,73	111	1	1	/	127	40	56	48
23	p.N34S	missense	0,43	142	/	/	/	480	75	94	83
24	V165I	missense	0,44	NA	/	/	/	366	55	62	55
25	c.823G > A	missense	NA	NA	/	/	/	96	95	99	92

Total IQ: 67,82 (range 40-99)
Verbal IQ: 75,88 (range 45-118)
Performance IQ: 69,52 (range 98-45).

Cognitive level	N°	mean	range
Normal IQ (>85)	5	95,4	91-99
Borderline IQ (71-85)	6	78	74-84
Mild cognitive Impairment (70-51)	7	57,57	51-66
Moderate-Severe cognitive impairment (<50)	7	45,14	40-50

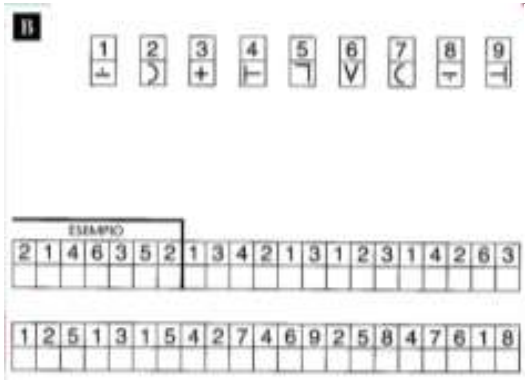
Discrepancy between Verbal and Performance IQ: 80% (20/25)

PIQ-VIQ discrepancy	N°	Cognitive level
< 10	12 (40%)	4 pt in Normal IQ 3 pt in Borderline IQ 2 pt in mild cognitive impairment 3 pt in moderate-severe cognitive impariment
>10	5 (20%)	1 pt in Normal IQ 1 pt in Borderline IQ 1 pt in mild cognitive impairment 2 pt in moderate-severe cognitive impariment
>20	3 (12%)	1 pt in Normal IQ 1 pt in Borderline IQ 1 pt in moderate-severe cognitive impariment

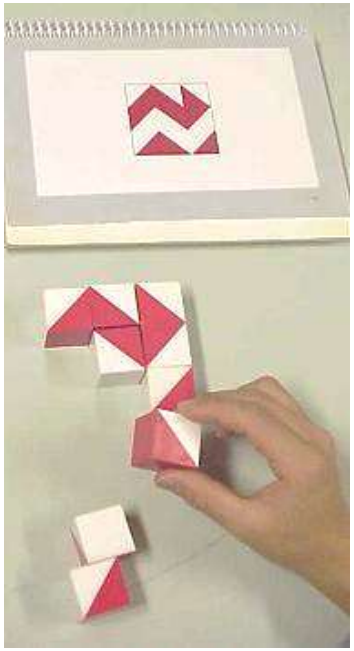
WISC-III scale (D. Wechsler, 2012)

pt	age	TIQ	VIQ	PIQ	CF	IN	CR_SN	SO_AN	SF	RA	DC	VC	RO	CO	MC	CI	LN	RM_ML	RS
1	65	99	104	98															
2	120	79	67	96															
3	118	43	54	45	1	3	1	5	3	1	4	5	2	2					
4	123	77	81	77	8	9	7	10	9	7	6	6	4	4					
5	161	48	59	48	5	2	3	4	1	3	1	7	3	4					
6	102	66	63	76	7	7	9	7	8	2	2	3	7	4					
7	235	45	45	45	2	1	2	2	2	2	1	2	1	1	1				
8	133	79	94	89															
9	221	50	65	45	5	4	2	3	1	2	1	1	1	3	8				
10	245	51	59	54	7	5	2	4	3	6	4	5	3	3	3				
11	144	55	62	55	5	3	5				1	4							
12	84	59	76	71			4	6			6	8		4	1	7	6	4	4
13	131	52	56	58	4	2	4	6	2	2	1	6	1	1					
14	163	84	118	74			2	13			7	14		12	9	6	8	5	5
15	184	56	82	63	2			4			1	9		8	5	7	2	5	3
16	366	55	62	55	8	3	3	4	3	6	3	4	3	5	3				
17	85	93	95	92															
18	87	46	53	51	2	2	1					1				3		2	
19	153	57	50	65															
20	480	75	94	83	5	10	4	8		6	8	9		4	9				
21	118	99	114	87			5	13			3	10		14	10	11	11	10	12
22	121	102	116	106			6	11			9	11		16	8	11	10	13	7
23	126	40	56	48			4	2			3	2		4	1	1	1	2	6
24	39	74	83	71		7					5		6						
total	158,5	66	75	69	5	8,5	4,75	8,5	3,55	6	5,6	8	6	9,5	7	7,6	7,3	8,3	8,3

Picture Completion
Measures ability to observe details and recognize specific features of the environment (whole to part discrimination). Also measures performance in deliberately focusing attention on a task.



Coding-Digit Symbol
Measures visual-motor speed and complexity and motor coordination.



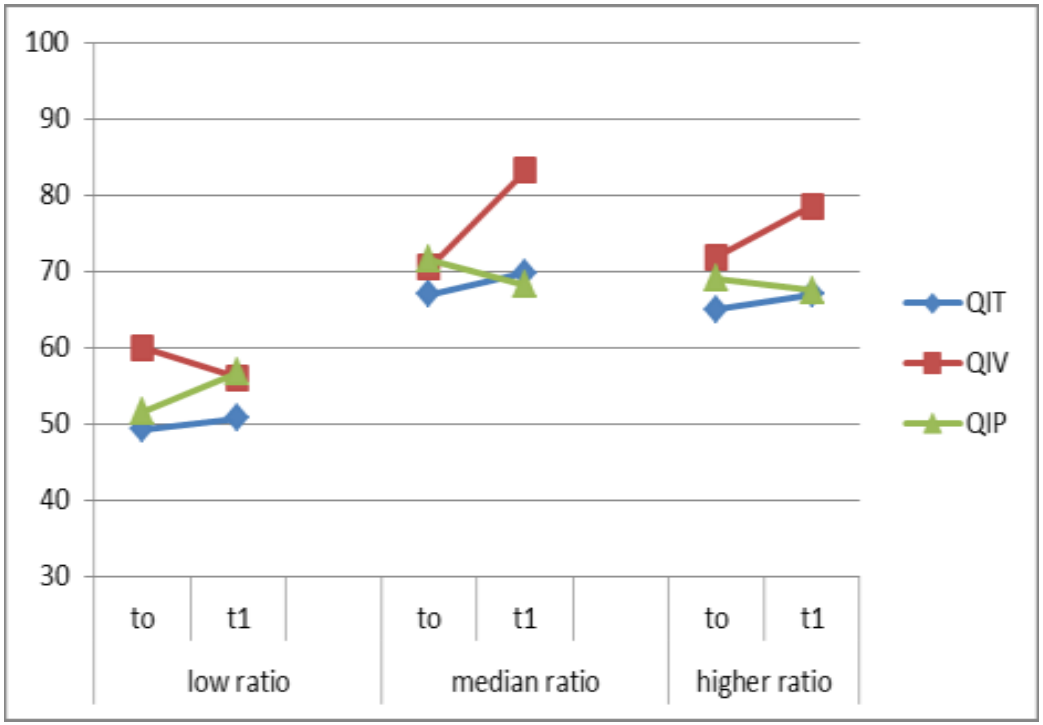
Block Design: Measures spatial problem-solving and manipulative abilities, and fluid intelligence . Part to whole organization describes one's skills in mentally "putting together" complex objects by seeing and mentally manipulating it's individual parts.

Picture Arrangement: Measures nonverbal reasoning and sequencing skills, and grasp of social cause and effect (also known as social intelligence).

Intellectual disability and Ketogenic Diet

	T0: before KD				T1: 18 months				T2: 36 months		
	T0 TIQ	VIQ	PIQ		T1 TIQ	VIQ	PIQ		T2 TIQ	VIQ	PIQ
normal IQ											
1	99	104	98		97	106	98		98	109	87
borderline IQ											
1	79	94	89		75	94	71				
2	79	67	96	↑	89	86	94		85	82	104
3	77	81	77		75	89	66	↑	81	100	80
Mild ID											
1	66	63	76	↑	72	98	58	↑	79	88	76
2	63	75	59		55	62	55				
3	59	76	71	↑	73	78	98				
4	52	56	58		50	60	58				
5	51	59	54	↑	60	69	59				
Moderate ID											
1	50	65	45		45	45	45				
2	48	59	48	↑	52	58	56		53	76	63
3	45	45	45		45	47	45				
4	43	54	45		40	54	39	↑	55	82	58
5	44	55	45	↑	56	82	63				

CSF / Blood glucose ratio and IQ

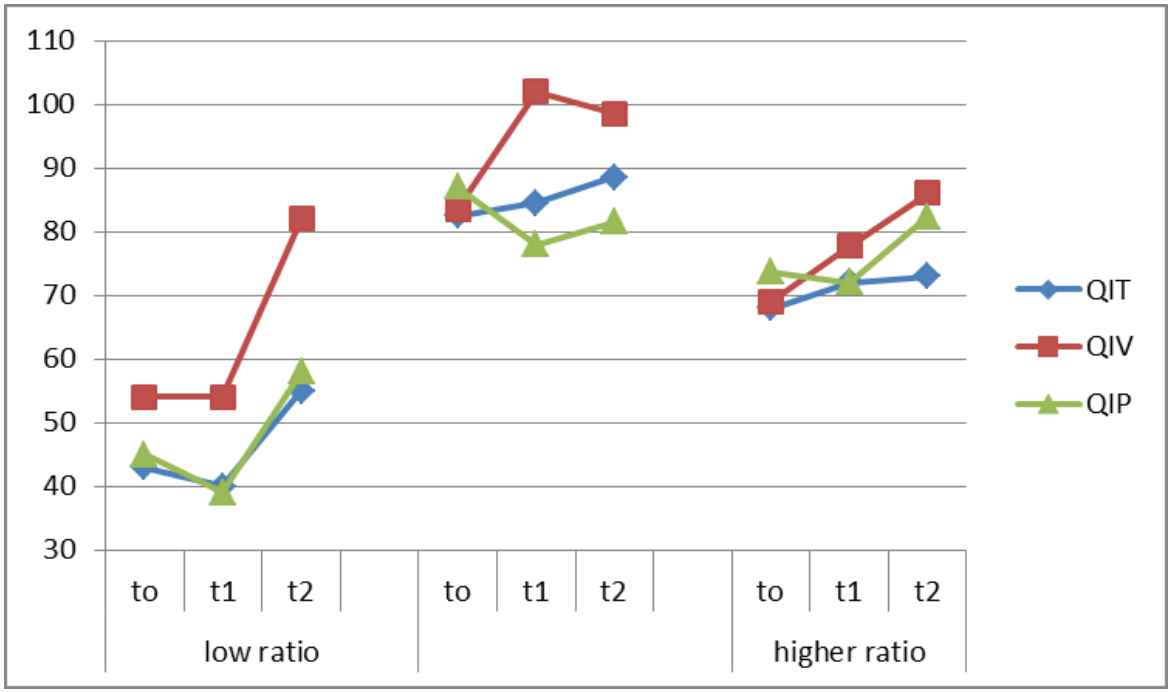


IQ avarage		TIQ	VIQ	PIQ
low ratio 0.33-0,35	to	49,25	60	51,5
	t1	50,75	56	56,75
median ratio 0,38-0,39	to	67	70,5	71,5
	t1	69,75	83,25	68,25
higher ratio 0.44-0,56	to	65	71,83	69
	t1	67	78,5	67,5

- N: 14
- low ratio: stationary TIQ, worsening in VIQ, improvement in PIQ
- middle and high ratio group: improvement in TIQ and VIQ, a worsening in PIQ

(p= 0,039)

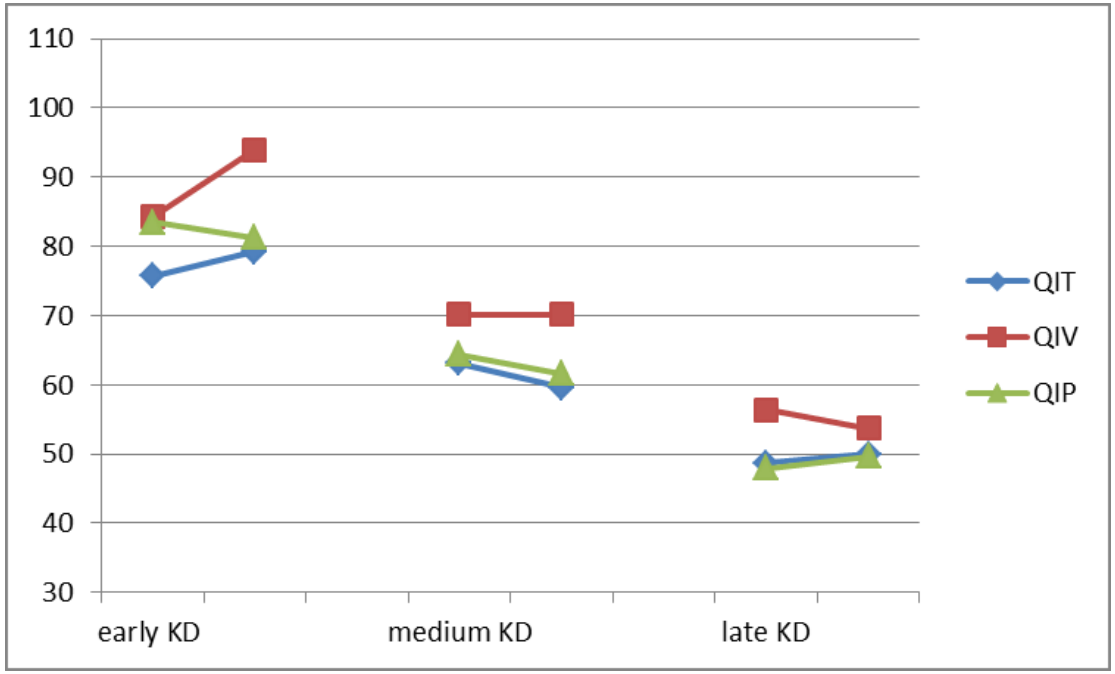
CSF / Blood glucose ratio and IQ



IQ avarage		TIQ	VIQ	PIQ
low ratio	to	43	54	45
	t1	40	54	39
	t2	55	82	58
median ratio	to	82,5	83,5	87
	t1	84,5	102	78
	t2	88,5	98,5	81,5
higher ratio	to	68	69	73,7
	t1	72	77,7	72
	t2	73	86	82,3

- N= 6 patients
- Follow-up: 36 months
- Low ratio: improvement in VIQ, PIQ and TIQ

Timing of Ketogenic Diet and IQ



	QIT	QIV	QIP
early KD < 6 years	75,75	84,25	83,5
	79,25	94	81,25
medium KD 6- 12 years	63,125	70,12	64,37
	59,57	70,14	61,57
late KD > 12 years	48,66	56,33	48
	50	53,66	49,66

- Early onset: imrpovement of TIQ and VIQ
- Medium onset: stable VIQ
- Late onset: decrease VIQ

(p= 0,015)

Conclusion

- ✓ Neuropsychological profile among patients with GLUT1DS varies differently from different phenotypes
- ✓ 81,5% Intellectual disability
  severe 18% - moderate 33% - mild 49%
- ✓ Most compromised: attention, executive functions, visuospatial and verbal memory
- ✓ Less data available about behavioural aspects
- ✓ Improvement after KD: visuo-motor precision, alertness, sensorimotor speed, performances
- ✓ Early introduction and duration of KD: impact on cognitive improvement

Conclusion: GLUT1DS and IQ

- ✓ Performances are the worst affected skills
- ✓ Attention, analysis and visual search skills, motor-graph performance, hand eye coordination, budgeting skills, problem solving
- ✓ GLUT1DS intellectual functioning similar to *Nonverbal Syndrome* characterized by a particular falling in performance tests and more specifically in the visual-spatial skills and coordination
- ✓ Easily derived within the GLUT1DS framework in which the motor aspects are more compromised and variably characterized by spasticity, dyskinesia, dysarthria, motor incoordination and paroxysmal movement disorder

Conclusion: ratio and IQ correlation

- ✓ better response to KD treatment in patients with higher ratio values in the short-term (18 months) that remains constant in the medium term (36 months)

- ✓ In medium term a positive response was also observed in patients with lower ratio values although not as significant as in the higher ratio group

→ need for longer duration of treatment and compensation of glucose in the CNS in patients with greater transporter defect

- ✓ KD: «the sooner the better»

- ✓ our data confirms the indication to continue the KD for a long period in order to increase the chances of recovery of intellectual disability

LONG TERM COMPLIANCE

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