Supplementary Material

Rapidly deteriorating course in Dutch Hereditary Spastic Paraplegia type 11 patients

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Illustrative long-term clinical follow-up of a SPG11 family (family 1 in Suppl. Table 1)

The consanguineous parents originating from Turkey had 11 children, two of whom died of an unspecified 'infectious disease' at age 6 months. Five of the nine surviving children developed complicated HSP (Figure S1). Age at onset of gait impairment, leg spasticity or learning difficulties was between 4 months and 20 years, after normal gestations and deliveries, and initially normal psychomotor development. The fifth child (patient II:5) has stayed in Turkey and has never visited a Dutch hospital, but some details from the history were available from a healthy sister. During follow–up, peripheral nerve and anterior horn cell degeneration developed with intrinsic hand muscle atrophy, confirmed by nerve conduction studies and nerve and muscle biopsies. The spastic paraplegia developed into a hypotonic weakness of the lower limbs, followed by the upper limbs, with serious flexion contractures. Learning disabilities developed in the same period, which forced them to switch to special needs education by the end of primary school. As cognitive decline progressed, language and verbal fluency became predominantly affected. Finally, the subjects lost spontaneous speech and after a disease duration of two to three decades they could only produce sounds. One patient also suffered a psychotic episode at age 24. Two subjects had mild cerebellar signs; extrapyramidal signs were absent.

Ultimately, all five patients became tetraplegic and completely wheelchair bound or bedridden, with severe dysphagia in at least two of them necessitating a percutaneous endoscopic gastrostomy (PEG) feeding tube. Two patients were obese and four had urinary incontinence, three of whom also had fecal incontinence. Four of the five affected siblings died of respiratory or cardiac complications, at ages 30 to 47. One of them is still alive, but is deteriorating rapidly.

Reviewing the brain MRIs – 15 years after the scans were made – revealed a thin corpus callosum and typical white matter changes, which led to a suspicion of SPG11. Subsequently, a homozygous pathogenic frameshift mutation was found in exon 6 (c.1203del; p. Asp402fs) in the two youngest affected siblings.

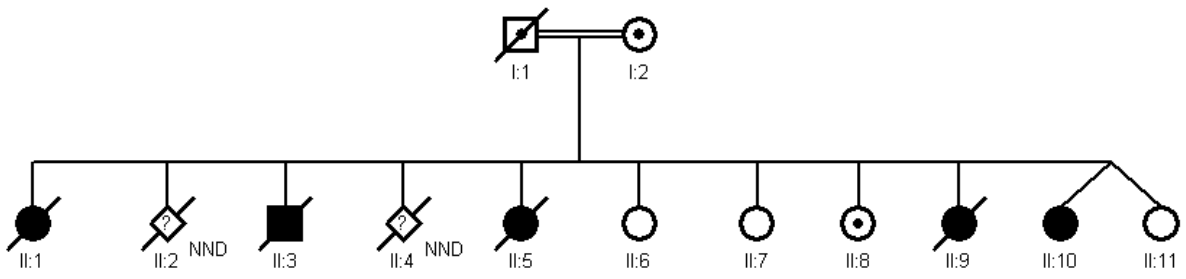

FIGURE S1: Pedigree of a Turkish family with consanguineous parents. Two children died at the age of 6 months, five children were affected by SPG11, of whom four have already died. Patient II:5 lived in Turkey and has never visited a Dutch hospital.

Supplementary Table 1. Clinical characteristics of 18 SPG11 patients.

Family /origin	ID/sex	Age at onset GI/leg spasticity (yr)	Age at onset LD (yr)	Symptom at onset	Age at last examination (yr)/ sex	Disease duration (yr) at most recent examination	Severity leg spasticity	Wheel-chair bound at age (GI duration) yr	Cognitive impairment	Behav. problems (age)	Hand muscle wasting	Peripheral neuropathy	Sphincter dysfunction	Dysarthria	Dysphagia	Cerebellar ataxia	Obesity	Abnormalities retinal pigment	Other	Cerebral MRI	Age at death	Cause of death
1 TU	1-II-1/V	4	<7	GI	26	22	severe	16 (12)	borderline-mild MR + cogn. decline	-	+	+	+++	n/a	n/a	n/a	-	-	joint contractures, pes equinus	n/a	30	Complication during surgery
	1-II-3/M	<1 (4 mths)	n/a	GI	24	24	Severe	7 (7)	borderline-mild MR + cogn. decline	Aggressive period	+	+	++A	-	+ (PEG drip feed) A	+	-	n/a	scapulae alatae, scoliosis, joint contractures, pes equinus, handtremor, **mutism,** EMG: motor neuron dysfunction	n/a	47	pneumonia
	1-II-9/V	12	9	LD	38	29	severe	25 (13)	borderline-mild MR severe cog decline	Psychosis (24 yr)	+	+	+++	+	+ (PEG drip feed)	+	++ ^	n/a	primary reflexes (snout, grip); pes excavates, joint contractures, **mutism**	TCC, WMA*, STA	38	pneumonia
	1-II-10/V	15	10	LD	37	27	severe	26 (11)	borderline-mild MR severe cogı decline	-	+	+	+++	+	-	-	++	n/a	bruxism, pes excavatus, joint contractures	TCC, WMA*, STA	N.A.	N.A.
2 NL	2-II-1/M	13	n/a	GI	29	16	severe	29 (16)	borderline MR + cogn. decline	-	n/a	-	+++A	+A	-	n/a	+A	n/a	amblyopic OS, aphasia	n/a	48	pneumonia
	2-II-3/M	14	n/a	GI	24	10	severe	23 (9)	borderline MR + cogn. decline	-	+	+	+++A	+A	+ (PEG drip feed)	n/a	+^	n/a	blindness (can only discriminate between light/dark), **mutism**	n/a	45	upper respiratory tract infection
	2-II-4/V	11	13	GI	46	35	severe	25 (14)	borderline MR + cogn. decline	-	+	+	+++	+	+	+	+^	-	Hypermetropia ODS, pes equines	n/a	N.A.	N.A.
3NL	3-V-1/V	14	8	LD	20	12	moderate	N.A.	borderline MR	PDD-NOS	n/a	-	-	-	-	-	+	n/a	fatigue	TCC, WMA*, STA	N.A.	N.A.
	3-V-2/M	14	8	LD	15	7	mild	N.A.	borderline MR	ADHD	n/a	-	+	-	n/a	n/a	+	n/a		TCC, WMA*	N.A.	N.A.

Family /origin	ID/sex	Age at onset GI/leg spasticity (yr)	Age at onset LD (yr)	Symptom at onset	Age at last examination (yr)/ sex	Disease duration (yr) at most recent examination	Severity leg spasticity	Wheelchair bound at age (GI duration) yr	Cognitive impairment	Behav. problems (age)	Hand muscle wasting	Peripheral neuropathy	Sphincter dysfunction	Dysarthria	Dysphagia	Cerebellar ataxia	Obesity	Abnormalities retinal pigment	Other	Cerebral MRI	Age at death	Cause of death
4 NL	4-II-1/V	12	n/a	GI	30	18	severe	28 (16)	cogn. decline	-	n/a	-	++	+	+	-	+	-	fatigue	n/a	N.A.	N.A.
	4-II-2/M	10	5	LD	28	23	severe	27(17)	moderate MR + cogn decline	Psychosis (26 yr)	n/a	-	++	+	-	+	+	+	myoclonus in adominal- and legmuscles ventricular tachycardia fatigue	n/a	N.A.	N.A.
	4-II-3/M	<10	<10	GI	28	18	severe	28 (18)	borderline-mild MR+ cogn decline	Psychosis (28 yr)	n/a	-	n/a	n/a	-	+	+	+		n/a	N.A.	N.A.
	4-II-4/V	11	11	GI	22	11	severe	N.A.	borderline-mild MR	-	-	-	+	n/a	+	-	++	-	fatigue	n/a	N.A.	N.A.
5 NL	5/M	<10	N.A.	GI	26	16	mild	N.A.	cogn. decline	PDD-NOS	-	-	+	+	-	+	++	n/a	EMG: motor neuron dysfunction	TCC, WMA*, STA	N.A.	N.A.
6 NL	6/M	8	n/a	GI	27	19	severe	22 (14)	cogn. decline	-	-	-	+	+	n/a	-	-	n/a	epilepsy as adult pes equinus	TCC, WMA*, STA	N.A.	N.A.
7 SO	7/M	2	<10	GI	15	13	mild	N.A.	mild MR	-	n/a	-	n/a	-	n/a	+	-	n/a	gynaecomastia	TCC, WMA*, STA	N.A.	N.A.
8 NL	8/M	22	4	LD	27	23	severe	24 (2)	moderate MR + cogn. decline	Psychosis (24 yr)	n/a	+	+++	+	+	+	+A	n/a	pes equines	TCC, WMA*, STA	N.A.	N.A.
9 NL	9/M	<8	2	LD	13	11	severe	15A (7)	mild MR + cogn decline	PDD-NOS	n/a	-	+	+	n/a	-	+	n/a	colour-blindness, myopia, hyperlaxity, cafe-au-lait spot, pedes plano valgis	TCC, WMA*	N.A.	N.A.

A: from history after last examination, ADHD: Attention-Deficit/Hyperactivity Disorder, EMG: electromyography, GI: gait impairment, LD: learning difficulties, MR: mental retardation according to Wechsler scale: IQ 90-110: normal, IQ 80-90: dull normal, IQ 70-79: borderline/ learning difficulties, IQ 50/55-70: mild MR, IQ 35/40-55: moderate MR, IQ 20/25-40: severe MR, n/a: not available, N.A.: not applicable, NL: from the Netherlands, Obesity: defined as: - BMI< 25, + BMI 25-30, ++ BMI >30,

^: before dysphagia, PDD-NOS: Pervasive Developmental Disorder Not Otherwise Specified, PEG: percutaneous endoscopic gastrostomy, Sphincter dysfunctions: - no symtoms, + urinary urge, ++ urinary incontinence, +++ urinary and fecal incontinence, SO: from Somalia, TU: from Turkey,

Cerebral MRI: STA: supratentorial atrophy, TCC: thin corpus callosum, WMA: white matter abnormalities *typical “ears of the lynx sign”