J Inherit Metab Dis (2013) 36:859–868
DOI 10.1007/s10545-012-9560-4

ORIGINAL ARTICLE

Krabbe disease in adults: phenotypic and genotypic update from a series of 11 cases and a review

Rabab Debs · Roseline Froissart · Patrick Aubourg · Caroline Papeix · Claire Douillard · Bertrand Degos · Bertrand Fontaine · Bertrand Audoin · Arnaud Lacour · Gérard Said · Marie T. Vanier · Frédéric Sedel

Received: 19 August 2012 / Revised: 23 October 2012 / Accepted: 25 October 2012 / Published online: 30 November 2012

Abstract Krabbe disease usually presents as a severe leukodystrophy in early infancy and childhood. From a series of 11 patients and 30 cases previously reported in the literature we describe the clinical, radiological, electrophysiological and genetic features of adult Krabbe disease. Patients diagnosed after the age of 16 years were included in this study. They were further divided into three groups depending on age at symptoms onset: (1) childhood onset cases (n=7); (2) adolescence onset cases (n=6) and adult onset cases (n=28). Overall, 96 % of patients in the adult-onset group presented with signs of pyramidal tracts dysfunction. Spastic paraparesis or tetraparesis became prominent in all cases. A peripheral neuropathy was present in 59 % of cases and was most often demyelinating (80 %). Other clinical signs encompassed dysarthria (31 %), cerebellar ataxia (27 %), pes cavus (27 %), deep sensory signs (23 %), tongue atrophy (15 %), optic neuropathy (12 %), cognitive decline (12 %). Cerebrospinal fluid protein concentration was moderately increased in 54 % of patients. Patients in the adolescent- and childhood-onset groups had

Communicated by: Nicole Wolf

R. Debs · C. Papeix · B. Degos · B. Fontaine · G. Said · F. Sedel
Department of Neurology, Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris and University Pierre&Marie Curie, Paris, France

R. Froissart · M. T. Vanier
Laboratoire des Maladies Héréditaires du Métabolisme et Laboratoire Gillet-Mérieux, Groupe Hospitalier Est, Hospices Civils de Lyon, 69500 Bron, France

P. Aubourg
Department of Pediatric Neurology, CHU Kremlin Bicêtre, Assistance Publique–Hôpitaux de Paris, France and INSERM UMR745, University Paris-Descartes, Paris, France

C. Douillard
Service d'endocrinologie et maladies métaboliques, Clinique endocrinologique Marc Linquette, CHU de Lille, France

B. Fontaine
Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, INSERM, UMR 546, Paris, France

B. Audoin
Department of Neurology, CHU de la Timone, Marseille, France

A. Lacour
Service de Neurologie D et Centre de réference des maladies rares neuromusculaires, C.H.R.U Lille, Lille, France

M. T. Vanier
INSERM, Unité 820, Faculté de Médecine Lyon Est, Université Lyon-1, Lyon, France

F. Sedel
Neurometabolic unit, reference center for lysosomal diseases, GRC13-UPMC, Paris, France

F. Sedel (✉)
Department of Neurology, Hôpital de la Salpêtrière, 47 Boulevard de l'Hôpital, 75651 Paris cedex 13, France
e-mail: frederic.sedel@psl.aphp.fr

similar presentations but were more likely to display optic neuropathy (33 % and 57 %) and cerebellar ataxia (50 % and 57 %). In the adult-onset group, the disease progressed slowly over more than 10 years, but a rapid course was observed in two patients. Abnormalities of brain MRI was similar in the three groups and included high signals of cortico-spinal tracts (94 % of cases), hyper-intensities of optic radiations (89 %) and hyper-intensities or atrophy of the posterior part of the corpus callosum (60 %). No clear genotype-phenotype relationship could be demonstrated.

Introduction

Krabbe disease also called globoid cell leukodystrophy (GLD, OMIM #245200) is an autosomal recessive lysosomal storage disease resulting from a deficiency of the lysosomal enzyme galactocerebrosidase (galactosylceramidase, GALC) (Suzuki and Suzuki 1970; Wenger et al 2001). The deficiency of GALC impairs the degradation of a major myelin lipid, galactocerebroside and that of a parent cytotoxic compound, galactosylsphingosine also called psychosine (Suzuki 1998). The excess of galactosylceramide elicits the formation of multinucleated macrophages, the globoid cells. Progressive accumulation of psychosine has been well established in infantile Krabbe disease and in mouse, dog and monkey animal models; it can explain the prominent death of oligodendrocytes and myelination arrest, and contributes to progressive demyelination (Suzuki 1998; Svennerholm et al 1980). Four different forms of Krabbe disease are usually distinguished based on age at onset of neurological symptoms: (1) the early infantile form starts between 3 and 6 months and is characterized by hyperirritability, stagnation of development, blindness, hypertonicity, and decerebrate rigidity. Death occurs between the 1st and the 3rd years of age (Hagberg et al 1963; Hagberg et al 1969); (2) the late infantile form (onset between 7 months-12 months) and (3) the juvenile form (onset between 1 and 10 years) are characterized by spastic tetraparesis, cerebellar ataxia, optic atrophy, mental retardation and cognitive decline (Lyon et al 1991). In contrast, the adult form has been rarely reported. It is a more insidious disease with heterogeneous phenotypes, mostly described as isolated case reports. Here, from a series of 11 patients diagnosed in French hospitals and 30 cases previously reported in the literature (Bajaj et al 2002; Bernardini et al 1997; De Stefano et al 2000; Farina et al 2000; Grewal et al 1991; Harzer et al 2002; Henderson et al 2003; Jardim et al 1999; Kapoor et al 1992; Kolodny et al 1991; Luzi et al 1996; Sabatelli et al 2002; Satoh et al 1997; Thomas et al 1984; Turazzini et al 1997; Verdru et al 1991; Wang et al 2007), we attempt to describe the clinical, radiological, electrophysiological, biochemical and genetic features of adult Krabbe disease.

Methods

All patients diagnosed in France with Krabbe disease after the age of 16 years in a single laboratory (MTV and RF) were included in this study. This criterion encompassed patients with symptoms starting in adulthood (true adult form) as well as patients with symptoms starting in childhood or adolescence but who were diagnosed only when they were adults. Patients were subsequently divided into three groups according to age at onset: (1) childhood onset (<10 years); (2) adolescence onset (11–15 years) and adult onset (≥16 years). The diagnosis was confirmed by deficient galactocerebrosidase activity in leucocytes or fibroblasts. Sequencing of all exons and exon-intron boundaries of the *GALC* gene was performed in 10/11 cases. Six patients (*Patients #1,3,4,9,10,11)* were seen in the same center (Pitié-Salpêtrière Hospital). For the other patients, clinical and imaging data were collected retrospectively by contacting referent neurologists. When the patient's early history had previously been published (patients # 2,4,5,8) (Bataillard et al 1997; Fontaine et al 2003; Phelps et al 1991), updated clinical data were obtained from referent neurologists. A review of the literature was performed using the NIH Pubmed database and the authors' own bibliography. Only articles published in English or French were included. Cases with insufficient clinical description were excluded. Clinical signs were considered absent when they were not mentioned in corresponding articles. MRI data were included only when the corresponding images were shown in the article or when the MRI was sufficiently described in the text. Several cases published more than once were excluded by careful perusal of publications. Cases from the World-Wide Registry for Krabbe Disease published recently were not included in the present study because of insufficient details in clinical and MRI description (Duffner et al 2012). The latter study is however discussed.

Results

Brief summary of our cases

Patients with onset in childhood (<10 years)

Patient#1: This 22 year-old man, originating from Senegal, presented with walking difficulties since the age of 4. He progressively developed pes cavus, kyphosis and progressive motor weakness in lower and upper limbs. At 20 years of age, he became wheelchair-bound. On examination, he had diffuse amyotrophy, pes cavus, asymmetric motor weakness, pyramidal spasticity and hypopallesthesia in lower limbs. His MRI is described in Fig. 1.

Patient#2: Her initial history was reported by Phelps et al (Phelps et al 1991). This 36 year-old woman of French ancestry came to medical attention at the age of 5 years when visual acuity decreased in both eyes. She progressively developed spastic paraparesis with motor weakness, generalized dystonia, cerebellar signs and dysarthria. She became wheelchair-bound at the age of 12 years. She currently displays severe cognitive decline and is totally dependent for activities of daily living. She is the younger sister of patient#5.

Patients with onset in adolescence (11–15 years)

Patient#3: This 24 year-old woman originating from the Reunion Island developed walking problems with left lower limb weakness at the age of 12 years. Neurological signs progressively worsened with asymmetric spastic paraparesis. Here MRI is reported on Fig. 1.

Patient #4: This now 70 year-old woman of French ancestry was previously reported by Fontaine et al (2003). She presented in adolescence with progressive spastic paraparesis. She became wheelchair-bound at the age of 59. Clinical and neurophysiological examination disclosed spastic paraparesis, demyelinating sensorimotor neuropathy, urinary incontinence but no cognitive impairment at the age of 61. Thereafter, her clinical condition worsened with progressive cognitive decline and total dependence in her activities.

Patients with onset in adulthood (>16 years)

Patient #5: This 39 year-old man of French ancestry is the older brother of patient #2. He had a more insidious disease course than his sister. Although he exhibited minor walking difficulty and slight decreased visual acuity since the age of 5, he only came to medical attention at the age of 16, after the diagnosis of Krabbe disease was established in his younger sister (Phelps et al 1991). At this age, he started to present spastic paraparesis. Examination disclosed pale optic discs with a normal intellectual development. His neurological symptoms slowly progressed and at the age of 38, he displayed spastic paraparesis, and upper-limbs dysmetria. He could still walk unaided and had no intellectual decline.

Patient#6: This 40 years old woman of French ancestry complained from right lower limb weakness at the age of 22. She progressively presented tetraparesis and severe dysarthria leading to mutism. She lost the ability to walk at the age of 40.

Patient#7: This 25 year-old Italian woman came to medical attention because of lower limbs spasticity that appeared at the age of 24. At neurological

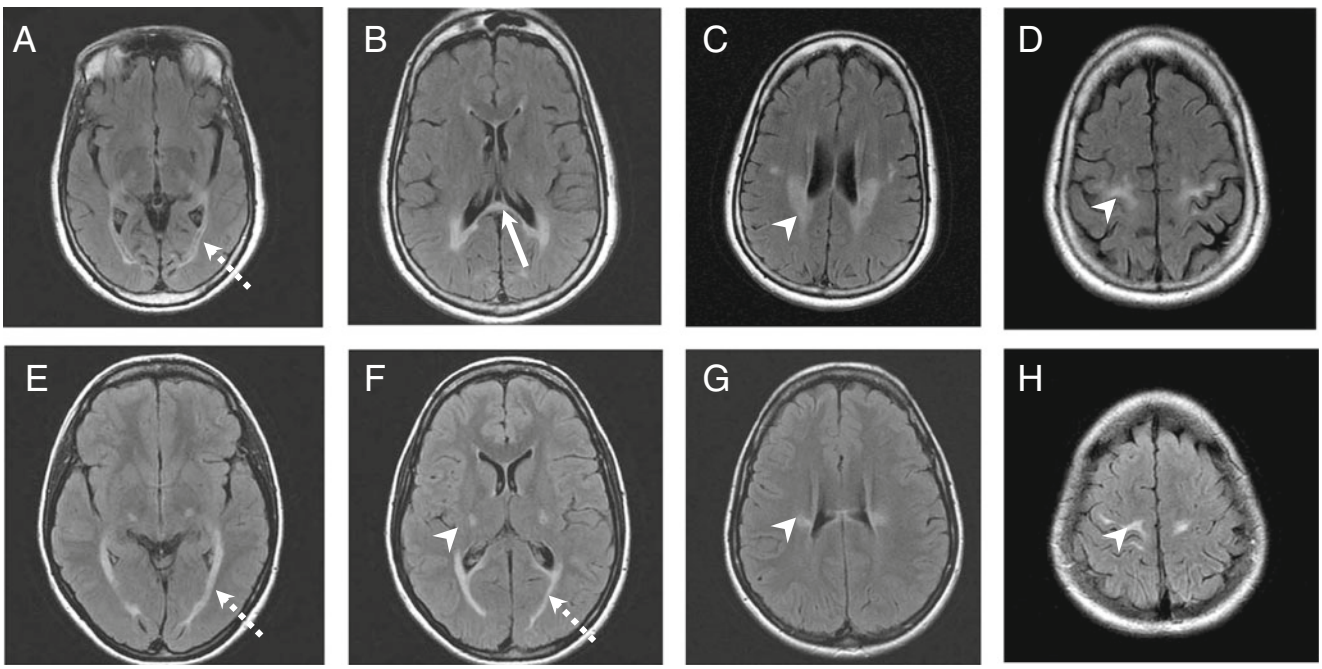

Fig. 1 Brain MRI of patients numbered 1 (**a**–**d**) and 3 (**e**–**h**) showing the T2-Flair hyperintensities of the pyramidal tract (*arrow heads*), splenium of the corpus callosum (*white arrows*) and optic radiations (*dotted arrows*)

examination, isolated spastic paraparesis with brisk reflexes in four limbs was noticed.

Patient#8: This 56 year-old Turkish woman has been previously reported by Bataillard et al (1997). From the age of 25, she developed asymmetric paraparesis that progressed slowly. She currently has to use a wheelchair outside home.

Patient#9: This 54 year-old woman reported slight difficulties in practicing sports since childhood but frank neurological impairment appeared at the age of 50 when she noticed walking problems. Since then, she developed motor weakness in her four limbs. At examination, cerebellar dysmetria was noticed as well as signs of peripheral neuropathy with deep sensory loss and abolished ankle reflexes.

Patient#10: This 58 year-old man originating from the Caribbean Islands presented progressive lower limbs weakness since the age of 52. Neurological examination disclosed lower limbs weakness and spasticity with bilateral Babinski signs.

Patient#11: This 72 year-old woman, originating from Morocco, presented with walking difficulties since the age of 66 years. Neurological examination showed motor weakness in lower limbs predominating on flexor muscles, no motor deficit in upper limbs and brisk tendon reflexes.

Overall patients' characteristics

Eleven patients from six different centers were included in this study. In addition, 30 cases fulfilling our inclusion criteria (see Methods) were found in the literature. Since our cohort of 11 patients and published cases were similar in terms of demographic characteristics and symptoms frequencies (Table 1), data from our series and from the literature were pooled.

Overall there were 20 males and 21 females from 31 families. Median age at onset of neurological symptoms was 23 years (4 to 66 years) whereas the median age at diagnosis was 33 years, i.e., 10 years after disease onset. Age at last follow up was 35 years (16 to 73 years). There were seven childhood-onset, six adolescent-onset and 28 adult-onset cases. Two patients were still asymptomatic at the age of diagnosis (patients # 40 and 41) but showed signs of pyramidal tract dysfunction at clinical examination. Clinical, radiological and genotypic characteristics of our patients and published cases are summarized in Tables 1, 2 and 3.

Signs at onset

In the adult-onset group (28 patients), two patients (#40 and 41) were seen in the context of asymptomatic familial investigation. In 96 % of patients, presenting symptoms were reminiscent of pyramidal tracts dysfunction. Gait impairment was the main presenting symptom and was attributed to spastic paraparesis in most cases, however, some patients diplayed asymmetric weakness starting in a lower-limb or hemiparesis. Besides walking disorders, other presenting signs included unilateral upper-limb weakness and lower-limb hypoesthesia.

Presenting symptoms were similar in the adolescent-onset group (Table 2) but additional presenting signs were encountered in the childhood onset group, including decreased visual acuity, cerebellar ataxia and peripheral neuropathy mimicking Charcot Marie Tooth disease.

Clinical signs during evolution

In the adult-onset group, *spastic paraparesis* became prominent in 96 % of cases. Other signs related to central nervous system dysfunction were found in a minority of patients and included dysarthria, cerebellar ataxia, optic pallor or optic neuropathy, and cognitive decline. However, only one patient had severe dementia after 13 years of disease progression. Peripheral neuropathy was diagnosed in 59 % after nerve conduction studies were performed (see below). Clinical signs were often limited to pes cavus, tongue atrophy or deep sensory signs whereas two patients had signs of small fiber neuropathy.

Clinical signs were similar in *the childhood-onset and juvenile-onset groups* except optic atrophy and cerebellar ataxia that seemed more frequent than in the adult-onset group. However the small number of patients precluded any robust statistical comparison.

Disability and clinical course

Within the 28 adult-onset patients, the disease was generally slowly progressive over more than 10 years, but a rapid evolution within 6 to 12 months was described in two patients (patients # 21 and 24). Six patients became wheelchair-bound (patients # 6, 8, 31, 34, 36 and 39) after a mean delay of 16 years of disease progression. Four patients have died: one patient died 14 years after the beginning of his disease due to respiratory failure (patient # 34), another one died at the age of 73 years due to pneumonia secondary to severe dysphagia (patient #39) and two patients died following bone marrow transplantation (patients # 22 and 23).

In childhood- and adolescent-onset groups, five patients (among seven for whom information was available), had to use a wheelchair (patients # 1, 2, 4, 14 and 15). Although symptoms were slowly progressive in most patients, one patient displayed a plateau after the development of severe optic atrophy at the age of 8 years and then progressive motor weakness in adulthood (patient #16).

Table 1 Pooled data from our series and from the literature

Patient number	Family number	Gender	Age of onset	Age at diagnosis	Age at description	First signs at onset	Spastic para or tetraparesis	Dysarthria	Cerebellar dysfunction	Pes Cavus	Altered vibration / proprioception	Optic atrophy/ pallor	Tongue atrophy / fasciculations	Urinary dysfunction	Dementia / mental retardation	Reference
1	1	M	4	21	22	SP	+	+	–	+	+	–	–	–	–	This report
2	2	F	5	13	36	Altered VA	+	+	+	–	–	+	–	–	+	Phelps et al, this report
3	3	F	12	24	24	LL weakness	+	–	–	–	–	–	–	+	–	This report
4	4	F	NA	61	70	SP/urinary urgency	+	–	+	+	+	–	+	+	+	Fontaine et al
5	2	M	16	16	39	SP/altered VA	+	–	+	+	–	+	–	–	–	
6	5	F	22	40	40	LL weakness	+	+	–	–	–	–	–	–	–	This report
7	6	F	24	25	25	SP	+	–	+	–	–	–	–	–	–	This report
8	7	F	25	39	56	SP	+	–	–	–	–	–	–	–	–	Bataillard et al
9	8	F	50	54	54	SP	+	+	+	–	+	–	–	–	–	This report
10	9	M	52	58	58	SP	+	–	–	–	–	+	–	–	–	This report
11	10	F	66	72	72	SP	+	–	–	–	–	–	–	+	+	This report
12	11	F	Ch	33	33	SP	+	–	–	+	+	–	–	–	–	Farina et al #1
13	11	M	Ch	35	35	SP	+	–	–	+	–	–	–	–	–	Farina et al #2
14	12	F	4	34	34	Ataxia	+	+	+	–	+	+	–	–	–	Thomas et al
15	13	F	6	NA	20	Hemiparsesis	+	+	+	+	–	+	–	–	–	Kolodny et al #8
16	14	F	8	25	28	Altered VA	+	–	+	–	+	+	–	–	–	Jardim et al
17	15	M	11	33	33	SP	+	+	–	–	+	–	–	+	–	Bajaj et al #1
18	16	M	13	37	37	Hemiparesis	+	–	+	–	–	–	–	–	–	Kapoor et al
19	17	M	13	NA	30	LL weakness	+	+	+	+	–	+	+	+	–	Kolodny et al #14
20	18	M	14	24	29	SP	+	+	–	–	–	+	+	–	–	Grewal et al
21	19	M	16	17	17	UL weakness	+	–	–	–	–	–	+	–	–	Bernardini et al #1
22	20 (twins)	F	17	NA	18	SP	+	–	–	+	–	–	–	–	–	Kolodny et al #9
23	20 (twins)	F	18	18	18	UL weakness	–	–	–	+	–	–	–	–	–	Kolodny et al#10
24	21	F	19	19	19	LL weakness	+	–	+	–	–	–	–	–	–	Verdru et al
25	22	F	23	29	29	LL weakness	+	–	–	–	–	–	–	–	–	Farina et al #3
26	22	M	23	27	27	LL weakness	+	–	–	–	–	–	–	–	–	Farina et al #4
27	23	F	23	28	28	LL weakness	+	–	–	–	–	–	–	–	–	Wang el.
28	15	M	32	32	32	SP	+	–	–	–	–	–	–	–	–	Bajaj et al #2
29	24	M	37	39	39	SP	+	–	–	–	–	–	–	–	–	Turazzini et al #1
30	25	F	38	51	51	SP	+	+	+	–	+	+	–	–	–	Satoh et al
31	26	M	41	NA	57	UL weakness	+	–	–	+	–	–	+	–	–	Sabatelli et al #2
32	27	F	42	44	44	SP	+	–	–	–	+	–	–	–	–	De Stefano et al

Table 1 (continued)

Patient number	Family number	Gender	Age of onset	Age at diagnosis	Age at description	First signs at onset	Spastic para or tetraparesis	Dysarthria	Cerebellar dysfunction	Pes Cavus	Altered vibration / proprioception	Optic atrophy/ pallor	Tongue atrophy / fasciculations	Urinary dysfunction	Dementia / mental retardation	Reference
33	28	M	43	48	48	Hemiparesis	+	–	–	–	–	–	–	–	–	Henderson et al
34	26	M	45	NA	51	UL weakness	+	–	–	–	–	–	–	–	–	Sabatelli et al #3
35	29	M	45	53	53	Hypoesthesia	+	+	+	–	+	–	–	–	+	Luzi et al
36	26	M	47	59	59	Motor weakness (central+ peripheral)	+	+	–	+	+	–	+	–	–	Sabatelli et al #1
37	30	M	50	62	62	SP	+	+	–	–	–	–	–	–	–	Harzer et al #1
38	30	M	50	63	63	SP	+	+	–	+	–	–	–	–	+	Harzer et al #2
39	31	F	NA	NA	73	SP	+	+	+	+	+	–	+	+	–	Kolodny et al #15
40	19	F	As	16	16	As	–	–	–	–	–	–	–	–	–	Bernardini et al #2
41	24	M	As	29	29	As	–	–	–	–	–	–	–	–	–	Turazzini et al #2
Percentages							97	38	36	33	31	23	18	15	13	

As asymptomatic, *LL* lower limbs, *NA* non avalable, *SP* spastic paraparesis, *UL* upper limbs, *VA* visual acuity, *Ch* childhood

MRI

In the adult onset group, detailed brain MRI data were obtained for 17 patients. T2-hyperintensities along the pyramidal tracts were present in 15/16 patients (94 %). Abnormalities of the whole tracts starting from pre-rolandic regions, corona radiata, internal capsules, cerebral peduncles, ventral portions of the pons and medulla were characteristic (Fig. 1) but sometimes abnormalities were incomplete or even asymmetric. Hyper-intensities along the optic radiations were observed in 8/9 patients (89 %). Hyper-intensities or atrophy of the splenium of the corpus callosum was seen in 9/15 patients (60 %). Longitudinal MRI follow-up was obtained for three patients only: brain abnormalities were stable for two patients after 1 and 6 years of follow-up (patients #21 and 25) but in another one (patient #8), MRI performed 13 years later showed worsening of sub-cortical atrophy.

Brain MR spectroscopy was performed in four patients (#6, 9, 27 and 32). Choline was considered normal in two patients (#6 and 9), increased in one (#32) and decreased in another one (#27). N-acetyl aspartic acid (NAA) was decreased in one patient (#27) and creatine was considered normal. Spinal cord MRI was performed in five patients (# 6, 9, 27, 28 and 29) and was considered to be normal.

In childhood- and juvenile-onset patients, abnormalities on brain MRI were similar to those described in the adult onset group (Fig. 1 and Table 3). Brain abnormalities were slowly progressive over 5 years for two patients (#15 and 20). Brain MR spectroscopy was done in two patients (#12, 13): choline was increased in both. NAA was normal in one and mildly reduced in the second.

Nerve conduction studies

Overall, 34 patients had nerve conduction studies. In the adult-onset group 59 % of patients had a pattern of polyneuropathy (versus 33 % in the adolescent-onset and 83 % in the childhood-onset groups). The polyneuropathy was demyelinating in 80 % of cases, and could be either of sensori-motor (65 %), purely sensory (10 %) or motor (5 %) types. In one patient (patient #39), the pattern was mixed (demyelinating and axonal) and in three patients (patient #19, 30 and 37), the type of polyneuropathy could not be specified. One patient (#1) had conduction blocks with dispersion leading to a misdiagnosis of chronic inflammatory demyelinating neuropathy. Treatment with intravenous immunoglobulins was not efficacious in this patient.

Multimodal evoked potentials

In adult-onset patients, Sensory evoked potentials (SEP) were obtained in seven patients (patients # 9, 10, 11, 21,

Table 2 clinical signs at onset and during disease's course

Presenting symptoms	Adult-onset (*n*=28)	Adolescent-onset (*n*=6)	Childhood- onset (*n*=7)
Spastic paraparesis	54 % (*n*=14)	50 % (*n*=3)	29 % (*n*=2)
Lower- limb weakness	19 % (*n*=5)	33 % (*n*=2)	0 %
Upper-limb weakness	15 % (*n*=4)	0 %	0 %
Hemiparesis	4 % (*n*=1)	17 % (*n*=1)	14 % (*n*=1)
Motor weakness (peripheral+central)	4 % (*n*=1)	0 %	14 % (*n*=1)
Hypo-esthesia	4 % (*n*=1)	0 %	0 %
Ataxia	0 %	0 %	14 % (*n*=1)
Altered visual acuity	0 %	0 %	29 % (*n*=2)
Symptoms during evolution			
Spastic paraparesis	96 % (*n*=25)	100 % (*n*=6)	100 % (*n*=7)
Peripheral neuropathy	59 % (13/24)	33 % (2/6)	83 % (5/6)
Dysarthria	31 % (*n*=8)	50 % (*n*=3)	57 % (*n*=4)
Cerebellar ataxia	27 % (*n*=7)	50 % (*n*=3)	57 % (*n*=4)
Pes cavus	27 % (*n*=7)	17 % (*n*=1)	43 % (*n*=3)
Deep sensory signs	23 % (*n*=6)	33 % (*n*=2)	71 % (*n*=5)
Tongue atrophy/ fasciculations	15 % (*n*=4)	50 % (*n*=3)	0 %
Optic atrophy	12 % (*n*=3)	33 % (*n*=2)	57 % (*n*=4)
Cognitive decline	12 % (*n*=3)	17 % (*n*=1)	14 % (*n*=1)
Urinary dysfunction	8 % (*n*=2)	67 % (*n*=4)	0 %

24, 28 and 29). They were abnormal in all cases (100 %) with prolonged central latencies either at the spinal or cerebral levels. *Visual evoked potentials* were performed in ten patients (patients # 8, 10, 11, 21, 24, 27, 29, 32 and 40), and were abnormal in three of them (30 %). *Brainstem auditory potentials* were recorded in eight patients (patients # 9, 10, 11, 21, 24, 28, 29 and 40) and were abnormal in three of them (37.5 %).

Cerebrospinal fluid analysis

A lumbar puncture was performed in 22 patients (13 adult-onset cases and nine adolescent/childhood-onset cases). The protein level was increased in 54 % of adult-onset cases and in 44 % of the adolescent/childhood-onset cases with a mean level of 0.5 g/L (0.13 to 0.77 g/L). Intrathecal synthesis of immunoglobulins was never observed.

GALC enzyme activities

All the patients studied (own and literature cases) exhibited a clear deficiency in GALC activity. Actual levels could not be compared due to differences in methodology. In our patients (#1 to 11), GALC activity was measured (generally in leukocytes) using a natural tritium-labeled galactosylceramide substrate (Vanier et al 1981), except for patients #6 and 7 who were tested using a C8-beta-D-galactosylceramide substrate coupled to tandem mass spectrometry (De Jesus et al 2009; Zhang et al 2010). Both methods were used in parallel for patients #1, 3, 6, 7 and 11.

Molecular analysis

Mutations were studied in 33 patients from 24 families (nine multiplex families, see Table 3). One allele remained unidentified in one of our patients (#1) after sequencing of the coding regions, and in three patients from the literature (#17, 28, 33) for whom only the deletion of 30 kb was tested. To facilitate comparison with most published mutations, the historical mutation nomenclature has been followed throughout this report.

A deletion of 30 kb starting in intron 10 and including the 3′ end of the GALC gene (always associated with the polymorphism 502C>T) was found in a compound heterozygous state in 20 adult-onset patients (60.6 %) from 12 families. This deletion constituted 30 % of all studied mutant alleles and 26 % of family alleles. In addition, several mutations were found more than once: G270D in six families (nine patients); Y303C in three families (five patients); G49G – a mutation affecting the last nucleotide of exon 1 and leading to missplicing- in three families (four patients); and T96A in two families (two patients). Each of the other mutations identified in this cohort was found in one single family: T51I, R63H, G95S, K123del, P138R, D171V, E215K, K343AfsX3, T513M, R515C, G537R, M617T, L618S, G622S, L629R. The mutations R515C, L618S and L629R were present in a homozygous state. T51I (c.152C>T), P138R (c.413C>G) and G622S (c.1864G>A) are novel mutations.

The frequent (35–45 % of alleles) 1637T>C polymorphism is known to significantly decrease the GALC activity

Table 3 *GALC*mutations and 1637T>C polymorphic background in adult-onset patients

Patient case number	Family number	Mutations	1637T>C Polymorphic background	References
1	1	G49G (missplicing)/?	T/C	This report
2	2	30 kb del / Y303C	del/T	Phelps et al, this report
3	3	30 kb del / Y303C	del/T	This report
4	4	G270D / T513M	C/C	Fontaine et al, this report
5	2	30 kb del / Y303C	del/T	Phelps et al this report
6	5	T96A / **P138R**	T/C	This report
7	6	30 kb del / **G622S**	del/C	This report
8	7	**T51I** / **K123del**	T/C	Bataillard et al, this report
9	8	30 kb del / G270D	del/C	This report
10	9	not done	not done	This report
11	10	G49G / G49G (missplicing)	C/C	This report
12	11	30 kb del / M617T	NA	Farina et al #1
13	11	30 kb del / M617T	NA	Farina et al #2
14	12	NA	NA	Thomas et al
15	13	30 kb del / E215K	del/C	Kolodny et al #8, De Gasperi et al 1996
16	14	L629R / L629R	T/T	Jardim et al
17	15	30 kb del / unknown	NA	Bajaj et al #1
18	16	NA	NA	Kapoor et al
19	17	NA	NA	Kolodny et al #14
20	18	NA	NA	Grewal et al
21	19	G49G (missplicing) / G95S	NA	Bernardini et al #1
22	20 (twins)	30 kb del / R63H	del/C	Kolodny et al #9, De Gasperi et al 1996
23	20 (twins)	30 kb del / R63H	del/C	Kolodny et al #10, De Gasperi et al 1996
24	21	NA	NA	Verdru et al
25	22	30 kb del / Y303C	NA	Farina et al #3
26	22	30 kb del / Y303C	NA	Farina et al #4
27	23	R515C/R515C	C/C	Wang et al
28	15	30 kb del / unknown	NA	Bajaj et al #2
29	24	NA	NA	Turazzini et al #1
30	25	L618S / L618S	C/C	Satoh et al
31	26	30 kb del / G270D	NA	Sabatelli et al #2
32	27	G270D / K343AfsX3	NA	De Stefano et al
33	28	30 kb del / unknown	NA	Henderson et al
34	26	30 kb del / G270D	NA	Sabatelli et al #3
35	29	T96A / D171V	C/C	Luzi et al
36	26	30 kb del / G270D	NA	Sabatelli et al #1
37	30	30 kb del / G270D	del/C	Harzer et al #1
38	30	30 kb del / G270D	del/C	Harzer et al #2
39	31	G270D / G537R	T/C	Kolodny et al #15, De Gasperi et al 1999
40	19	G49G (missplicing) / G95S	NA	Bernardini et al #2
41	24	NA	NA	Turazzini et al #2

The patient numbering is as in previous Tables. Families have been numbered to facilitate identification of siblings. *NA* not available; ?: allele not identified after sequencing; Unknown : *GALC* gene not sequenced. Note that the large deletion of 30 kb (indicated here as 30kbdel) has now been renamed c.1161+6532_polyA+9kbdel, in agreement with the HGVS nomenclature. The 1637T>C polymorphism is also named I546T at the protein level. The nucleotide 1637T is included in the 30kbdel. Aminoacids on this Table are numbered as traditionally described (numbering from the second methionine of the signal sequence) and not according to the current HGVS nomenclature. Novel mutations are indicated in bold

and is one cause of GALC pseudodeficiency (Wenger 2000). It has constantly been found in a cis configuration with the G270D mutation (Wenger 2000) as further shown in our cases #2 and 9. The frequency of the 1637C allele was remarkably high: this polymorphism was present in 9/14 (64 %) of the evaluable alleles in families 1–10; and in

10/13 (**77** %) in families from the literature including five homozygous subjects.

Hematopoietic stem cell transplantation was performed in two patients (#22 and 23 reported in Kolodny et al 1991). They were twin sisters of an elder brother deceased at age 19 most likely from Krabbe disease. These patients were both transplanted in 1990 when 18 years old and within 2 years after their initial symptoms. They both died 2 months after the transplantation due to graft versus host disease.

Discussion

Here we provide an updated description of Krabbe disease in adults. This clinical description delineates important clinical, radiological and biological clues to the diagnosis and is complementary to recently published data from the World-Wide Registry for Krabbe Disease (Duffner et al 2012).

In all our subgroups, the clinical and radiological picture was quite stereotypical with slowly progressive pyramidal tract dysfunction and a specific pattern of leukoencephalopathy involving the cortico-spinal tracts and, eventually, optic radiations and splenium of the corpus callosum. This pattern is highly suggestive of Krabbe disease, but can also be observed in adults with adrenoleukodystrophy (Sedel et al 2008). In contrast to what can be observed in the infantile form, cerebellar white matter and deep gray matter changes were only observed in patient #16 who had a childhood-onset disease. Cranial nerves or cauda equine enhancement that have been described recently in infantile Krabbe patients (Morana et al 2009) was not specifically assessed in our patients.

Only 59 % of the adult patients displayed signs of peripheral neuropathy which is in contrast with findings in the early infantile form, in which a peripheral demyelinating neuropathy is nearly constant (Husain et al 2004; Korn-Lubetzki et al 2003; Siddiqi et al 2006). Recently three additional cases of peripheral neuropathy in adults with Krabbe disease were reported (Malandrini et al 2012) demyelinating neuropathy was observed in one case and axonal neuropathy in two cases. Interestingly, typical intracytoplasmic inclusions that are usually found in the infantile form were absent in all three adult cases.

In general, siblings had quite similar clinical forms, but there were exceptions. For instance, association of the 30Kb deletion together with the Y303C mutation was associated with marked phenotypic differences within different families (e.g., families #2 and #22) and within the same family. For instance, in our family #2, patients #2 and #5 started to complain from decreased visual acuity at the age of 5, but the elder brother remained intellectually preserved with an active adult-life and moderate motor weakness, whereas his sister was already severely handicapped during childhood. Patients described by Bajaj (Bajaj et al 2002) showed similar heterogeneity: the first one (#17) with a juvenile-onset, had difficulty with sports since adolescence, while the second one (#28) lived normally until his 30s. On the other hand, all compound heterozygotes for the 30Kb deletion and the G270D mutation (genotype found in three different families and six patients) had an adult-onset and showed a peripheral neuropathy. Such a variability was also reported from analysis of the international registry (Duffner et al 2012). Nevertheless, while the concomitant occurrence among siblings of a late infantile form with an essentially adult onset form has been described (Phelps et al 1991; Verdru et al 1991), a multiplex family with an infantile form and a late onset form has to our knowledge never been reported.

As reported for the early onset forms of Krabbe disease (Rafi et al 1995), the 30 Kb deletion associated with a 502C>T polymorphism (Luzi et al 1995) is also the most common mutation described in the adult form, albeit always in a compound heterozygous state (Wenger 2000). From the present survey and other published studies, the presence of G270D or the missplicing G49G mutations appear predictive of a slowly progressive disease, whatever the nature of the associated allele. The mutations Y303C, G622S, M617T, E215K, L629R, R63H, R515C, L618S also seem associated with late onset forms. However, none of these mutations can be predictive of an adult-onset form.

Following a report showing initial good results of cord blood transplantation when performed at a pre-symptomatic stage of the infantile form (Escolar et al 2005), a newborn screening program has been implemented for Krabbe disease in New York state of the USA. The anticipated incidence of Krabbe disease was 1/100,000, with >90 % of patients expected to manifest the early infantile phenotype (Duffner et al 2012). After 5 years and >1,000,000 babies screened, only four babies (1/250000) were identified with early infantile Krabbe disease. Furthermore, 80 % of babies identified with low galactocerebrosidase activity and two mutations remained clinically unaffected (Duffner et al 2012). Thus, as for other lysosomal diseases, these results indicate that the proportion of late-onset forms had been largely underestimated. In parallel, a World-Wide Registry for Krabbe Disease was established. In June 2011, 122 patients were entered in the registry and seven of them (5.7 %) exhibited an adolescent or adult-onset (Duffner et al 2012). Reported data were consistent with our findings and clinical presentations as well as clinical course were similar to our patients. In our experience, adult cases represent 8 % of cases diagnosed in a single laboratory (MT Vanier, personal observations), however, as for other adult forms of inherited metabolic diseases, it is likely that many cases remain misdiagnosed.

Conflict of interest None.

References

Bajaj NP, Waldman A, Orrell R, Wood NW, Bhatia KP (2002) Familial adult onset of Krabbe's disease resembling hereditary spastic paraplegia with normal neuroimaging. J Neurol Neurosurg Psychiatry 72:635–638

Bataillard M, Richard P, Rumbach L, Vanier MT, Truttmann M (1997) Isolated spastic paraparesis disclosing Krabbe disease in adult age. Rev Neurol (Paris) 153:347–350

Bernardini GL, Herrera DG, Carson D et al (1997) Adult-onset Krabbe's disease in siblings with novel mutations in the galactocerebrosidase gene. Ann Neurol 41:111–114

De Gasperi R, Gama Sosa MA, Sartorato EL et al (1996) Molecular heterogeneity of late-onset forms of globoid-cell leukodystrophy. Am J Hum Genet 59:1233–1242

De Gasperi R, Gama Sosa MA, Sartorato E, Battistini S, Raghavan S, Kolodny EH (1999) Molecular basis of late-life globoid cell leukodystrophy. Hum Mutat 14:256–262

De Jesus VR, Zhang XK, Keutzer J et al (2009) Development and evaluation of quality control dried blood spot materials in newborn screening for lysosomal storage disorders. Clin Chem 55:158–164

De Stefano N, Dotti MT, Mortilla M et al (2000) Evidence of diffuse brain pathology and unspecific genetic characterization in a patient with an atypical form of adult-onset Krabbe disease. J Neurol 247:226–228

Duffner PK, Barczykowski A, Kay DM et al (2012) Later onset phenotypes of Krabbe Disease: results of the world-wide registry. Pediatr Neurol 46:298–306

Escolar ML, Poe MD, Provenzale JM et al (2005) Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med 352:2069–2081

Farina L, Bizzi A, Finocchiaro G (2000) MR imaging and proton MR spectroscopy in adult Krabbe disease. AJNR Am J Neuroradiol 21:1478–1482

Fontaine B, Thenin JP, Viader F (2003) Gait disorders with insidious progression in a 60-year old woman. Rev Neurol (Paris) 159:695–699

Grewal RP, Petronas N, Barton NW (1991) Late onset globoid cell leukodystrophy. J Neurol Neurosurg Psychiatry 54:1011–1012

Hagberg B, Sourander P, Svennerholm L (1963) Diagnosis of Krabbe's infantile leucodystrophy. J Neurol Neurosurg Psychiatry 26:195–198

Hagberg B, Kollberg H, Sourander P, Akesson H (1969) Infantile globoid cell leukodystrophy (Krabbe's disease). A clinical and genetic study of 32 Swedish cases 1953–1967. Neuropadiatrie 1:74–88

Harzer K, Knoblich R, Rolfs A, Bauer P, Eggers J (2002) Residual galactosylsphingosine (psychosine) beta-galactosidase activities and associated GALC mutations in late and very late onset Krabbe disease. Clin Chim Acta 317:77–84

Henderson RD, MacMillan JC, Bradfield JM (2003) Adult onset Krabbe disease may mimic motor neurone disease. J Clin Neurosci 10:638–639

Husain AM, Altuwaijri M, Aldosari M (2004) Krabbe disease: neurophysiologic studies and MRI correlations. Neurology 63:617–620

Jardim LB, Giugliani R, Pires RF et al (1999) Protracted course of Krabbe disease in an adult patient bearing a novel mutation. Arch Neurol 56:1014–1017

Kapoor R, McDonald WI, Crockard A, Moseley IF (1992) Clinical onset and MRI features of Krabbe's disease in adolescence. J Neurol Neurosurg Psychiatry 55:331–332

Kolodny EH, Raghavan S, Krivit W (1991) Late-onset Krabbe disease (globoid cell leukodystrophy): clinical and biochemical features of 15 cases. Dev Neurosci 13:232–239

Korn-Lubetzki I, Dor-Wollman T, Soffer D, Raas-Rothschild A, Hurvitz H, Nevo Y (2003) Early peripheral nervous system manifestations of infantile Krabbe disease. Pediatr Neurol 28:115–118

Luzi P, Rafi MA, Wenger DA (1995) Characterization of the large deletion in the GALC gene found in patients with Krabbe disease. Hum Mol Genet 4:2335–2338

Luzi P, Rafi MA, Wenger DA (1996) Multiple mutations in the GALC gene in a patient with adult-onset Krabbe disease. Ann Neurol 40:116–119

Lyon G, Hagberg B, Evrard P, Allaire C, Pavone L, Vanier M (1991) Symptomatology of late onset Krabbe's leukodystrophy: the European experience. Dev Neurosci 13:240–244

Malandrini A, D'Eramo C, Palmeri S et al (2012) Peripheral neuropathy in late-onset Krabbe disease: report of three cases. Neurol Sci doi:10.1007/s10072-012-0956-6

Morana G, Biancheri R, Dirocco M et al (2009) Enhancing cranial nerves and cauda equina: an emerging magnetic resonance imaging pattern in metachromatic leukodystrophy and krabbe disease. Neuropediatrics 40:291–294

Phelps M, Aicardi J, Vanier MT (1991) Late onset Krabbe's leukodystrophy: a report of four cases. J Neurol Neurosurg Psychiatry 54:293–296

Rafi MA, Luzi P, Chen YQ, Wenger DA (1995) A large deletion together with a point mutation in the GALC gene is a common mutant allele in patients with infantile Krabbe disease. Hum Mol Genet 4:1285–1289

Sabatelli M, Quaranta L, Madia F et al (2002) Peripheral neuropathy with hypomyelinating features in adult-onset Krabbe's disease. Neuromuscul Disord 12:386–391

Satoh JI, Tokumoto H, Kurohara K et al (1997) Adult-onset Krabbe disease with homozygous T1853C mutation in the galactocerebrosidase gene. Unusual MRI findings of corticospinal tract demyelination. Neurology 49:1392–1399

Sedel F, Tourbah A, Fontaine B, Lubetzki C, Baumann N, Saudubray JM, Lyon-Caen O (2008) Leukoencephalopathies associated with Inborn Errors of Metabolism in adults: a diagnostic approach. J Inherit Metab Dis 31:295–307

Siddiqi ZA, Sanders DB, Massey JM (2006) Peripheral neuropathy in Krabbe disease: effect of hematopoietic stem cell transplantation. Neurology 67:268–272

Suzuki K (1998) Twenty five years of the "psychosine hypothesis": a personal perspective of its history and present status. Neurochem Res 23:251–259

Suzuki K, Suzuki Y (1970) Globoid cell leucodystrophy (Krabbe's disease): deficiency of galactocerebroside beta-galactosidase. Proc Natl Acad Sci U S A 66:302–309

Svennerholm L, Vanier MT, Mansson JE (1980) Krabbe disease: a galactosylsphingosine (psychosine) lipidosis. J Lipid Res 21:53–64

Thomas PK, Halpern JP, King RH, Patrick D (1984) Galactosylceramide lipidosis: novel presentation as a slowly progressive spinocerebellar degeneration. Ann Neurol 16:618–620

Turazzini M, Beltramello A, Bassi R, Del Colle R, Silvestri M (1997) Adult onset Krabbe's leukodystrophy: a report of 2 cases. Acta Neurol Scand 96:413–415

Vanier MT, Svennerholm L, Månsson JE, Håkansson G, Boué A, Lindsten J (1981) Prenatal diagnosis of Krabbe disease. Clin Genet 20:79–89

Verdru P, Lammens M, Dom R, Van Elsen A, Carton H (1991) Globoid cell leukodystrophy: a family with both late-infantile and adult type. Neurology 41:1382–1384

Wang C, Melberg A, Weis J, Månsson JE, Raininko R (2007) The earliest MR imaging and proton MR spectroscopy abnormalities in adult-onset Krabbe disease. Acta Neurol Scand 116:268–272

Wenger DA (2000) Krabbe disease. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP (eds) GeneReviews™ [Internet]. University of Washington, Seattle

Wenger DA, Suzuki K, Suzuki Y (2001) Galctosylceramide lipidosis: globoid cell leukodystrophy (Krabbe disease). In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Vogelstein B (eds) The metabolic and molecular bases of inherited disease. McGraw Hill, New York, pp 3669–3694

Zhang XK, Elbin CS, Turecek F et al (2010) Multiplex lysosomal enzyme activity assay on dried blood spots using tandem mass spectrometry. Methods Mol Biol 603:339–350