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ORIGINAL ARTICLE

The natural history of Niemann–Pick disease type C in the UK

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Summary Niemann–Pick disease type C (NPC) is an autosomal recessive, neurovisceral lipid storage disorder. Mutations in two genes (*NPC1* and *NPC2*) produce indistinguishable clinical phenotypes by biochemical mechanisms that have not yet been entirely clarified. The wide spectrum of clinical presentations of NPC includes hepatic and pulmonary disease as well as a range of neuropsychiatric disorders. Late-onset disease has been increasingly recognized as the biochemical diagnosis of NPC has been more widely applied in adult neurology clinics. The clinical presentation and follow-up of 94 patients with NPC is described, 58 of whom were still alive at the time this report was prepared. The age at diagnosis ranged from the prenatal period (with hydrops fetalis) up to 51 years. This review of NPC patients in the UK confirms the phenotypic variability of this inherited lipid storage disorder reported elsewhere. Although a non-neuronopathic variant has been described, most patients in this series who survived childhood inevitably suffered neurological and in some cases neuropsychiatric deterioration. While symptomatic treatment, such as anticholinergic and antiepileptic drugs, can alleviate some aspects of the disease, there is a clear need to develop a specific treatment for this progressively debilitating neurodegenerative disorder.

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Abbreviations
NPC Niemann–Pick disease type C

Introduction

In view of the reported variability in phenotypes, this paper documents all the clinical data from known Niemann–Pick disease type C (NPC) patients in the UK. There are two genes involved in NPC (*NPC1* and *NPC2*); most patients (95%) have a mutation in the *NPC1* gene (Steinberg et al 1994; Vanier and Millat 2003). In the UK, the overwhelming majority of NPC patients have mutations in *NPC1*. As far as we are aware; this retrospective review includes only patients with defects in *NPC1*. Patients in whom no mutations in *NPC1* have been found, or on whom complementation studies have not been performed, have been further investigated to exclude defects in *NPC2*.

Diagnosis of NPC requires recognition of the protean presentations of this neurovisceral disorder, using ancillary testing to narrow the differential diagnosis and final confirmation by biochemical and genetic testing. The relevant tests are performed on cultured skin fibroblasts (Pentchev et al 1985). Confirmation of the diagnosis requires the combined demonstration of an intralysosomal accumulation of unesterified cholesterol with characteristic filipin staining and abnormal cholesterol homeostasis with impaired LDL-induced cholesterol esterification (Vanier et al 1991).

Subsequent analysis in the index case may reveal mutations that can be detected (or not) in future pregnancies.

Plasma chitotriosidase activity has been found to be modestly elevated (100–1500 μmol/L per h, normal 4–80) in affected patients and can be a helpful clue to diagnosis in a patient with a suggestive clinical picture (Imrie et al 2002).

Methods

We reviewed the case notes of all patients with NPC known to the patient database maintained by the Niemann–Pick Disease Clinical Nurse Specialist. This database holds demographic data on all UK patients diagnosed with NPC by filipin staining and/or esterification studies, and where available, mutation analysis. The review cohort was divided into three groups based on the age of presentation:

1. **Patients with neonatal presentation of NPC.** An early-onset (prenatal, perinatal, early infantile and late infantile). This is sometimes seen as a rapidly progressive form, associated with severe liver dysfunction and developmental delay in infancy (patients 1–10, Table 1). In those patients who survive the neonatal liver disease, this is followed by supranuclear gaze palsy, ataxia, increasing spasticity, seizures and dementia. The onset of neurological problems can occur at any time over years or even decades in this group of patients (Table 1).
2. **Patients presenting with NPC in childhood.** A juvenile or childhood-onset form, often correlating with the common *NPC1* mutation and characterized by mild learning difficulties in childhood, followed by a slowly progressive onset of supranuclear gaze palsy, ataxia, and spasticity. Gelastic seizures, cataplexy and complex epilepsies often occur in this group of patients and are difficult to control. Dementia usually occurs in the teenage years, but survival into adult life is common (Table 2).
3. **Adolescents and adults presenting with NPC.** A late-onset variant similar to juvenile-onset disease, but presenting for the first time in adolescence or adult life (Imrie et al 2002, Tables 3 and 4).

Table 5 has been included to highlight that variability can exist between siblings.

We report the clinical signs and symptoms at presentation and the subsequent clinical course of all known NPC patients in the UK. This is based on cases included between 1999 and 2006 in the patient database maintained by the Niemann–Pick Disease Group (UK) Clinical Nurse Specialist. All cases have had biochemical analysis at one of the three laboratories in the UK and/or France providing the service and have been referred or self-referred to the Nurse Specialist or Support Group. All UK laboratories and laboratories in Lyon, France have been involved in submitting data on cases they have diagnosed, but clinical data have not always been available.

Results

Almost equal numbers of patients presented in the neonatal period ($n = 33$), childhood ($n = 31$) or adolescence/adult life ($n = 30$). Ages at diagnosis, presenting symptoms and signs, disease progression and age at death are shown Tables 1–3. The *NPC1* allele mutations associated with each patient are detailed, where known.

Patients with neonatal presentation of NPC

NPC disease has been reported as the second most common genetic cause of liver disease in infancy in the UK after α_1-antitrypsin deficiency (Kelly et al 1994; Mieli-Vergani et al 1991). Neonatal jaundice without other overt signs of liver disease may herald a more aggressive clinical course, with neurological abnormalities appearing in the first 4 years of life. Children presenting with hypotonia and delayed motor development before 2 years invariably have hepatosplenomegaly, delayed walking, intention tremor and generalized spasticity and die between 3 and 5 years of age (Table 1, patients 1–10). Vertical supranuclear gaze palsy (VSGP) is not usually seen at this stage of the illness. This severe phenotype is most frequently recognized in patients from southern Europe, the Middle East and North Africa (Patterson et al 2001).

Thirty-three patients (20 female, 13 male) in the review cohort presented with neonatal liver disease and/or prolonged jaundice and were followed continuously until a diagnosis of NPC was reached. Summary information on all patients presenting in the neonatal period is shown in Table 1.

Patients presenting with NPC in childhood

Thirty-one patients (11 male, 20 female) were aged between 1 and 12 years at diagnosis (Table 2). Any neonatal signs and symptoms recorded in this table were noted retrospectively. In those with the classic presentation, about half have transient neonatal jaundice, with development in early childhood being usually unremarkable. The onset of neurological problems is usually in early school years .The affected child suffers increasing physical and intellectual disability through late childhood and adolescence, eventually becoming wheelchair-bound and incapable of continuing in school. Death, often from pulmonary complications, may occur in the teenage years or early adulthood (Patterson et al 2001).

Adolescent patients presenting with NPC

Sixteen patients (9 male, 7 female) were diagnosed with NPC between the ages of 12 and 23 years (Table 3), having presented as adolescents. This table represents those patients in

Table 1 Patients with neonatal presentation of NPC

Patient number	Sex	Age at which clinical signs were first noted	Age at diagnosis	Neonatal liver disease	Hepatosplenomegaly (HS)/ Splenomegaly (S)	Seizures	Vertical gaze palsy	Development	Ataxia	Swallowing problems	Mutations	Age at review /age at death†
1	F	Birth	9 mo	Jaundiced	S	None	No	Delayed at 3 y	No	No	4bpDel670 /DelTGCT (2005–2011)	3 y 6 mo
2	F	Birth	2 mo	Jaundiced	HS	None	No	Normal at 16 mo	No	No	I1061T/?	4 y
3	M	Birth	8 mo	Jaundiced	HS	None	No	Normal at 2 y 8 mo	No	No	I1061T/Del 10bp 962	4 y 8 mo
4	F	Birth	12 mo	No	S	None	No	Normal at 2 y 5 mo	No	No	I1061T/N222S /R958Q/IVS23 +4delA	4 y 8 mo
5	M	Birth	4 mo	Jaundiced	Yes++	None	5 y	Normal at 7 y	No	No	I1061T/R1059X	7 y
6	F	Birth	11 mo	Jaundiced	HS	C 5 y E 5 y 10 mo	3 y	Delayed	Severe	No	T1036M/R1086H	8 y
7	F	Birth	11 mo	Jaundiced	HS	C 5 y E 5 y 10 mo	3 y	Delayed	Severe	No	T1036M/R1086H	7 y
8	F	Birth	4 mo	Jaundiced LD	HS	C 2 y 11 mo	Not noted	Delayed at 18 mo	Severe	1 y 10 mo		3 y 4 mo†
9	M	Birth	9 mo	Jaundiced LD	HS	C 4 y E 7 y	4 y	Delayed from 1 y	<5	5 y	I1061T/?	9 y†
10	M	Birth	4 mo	Jaundiced LD	HS	N/A	N/A	Delayed from birth	N/A	N/A		4 mo†
11	F	Birth	9 mo	Jaundiced LD		Yes	<6 y	<6 y	6 y 5 mo		I1061T/?	9 y†
12	M	Birth	10 mo	Jaundiced LD	S	C 4y 9 mo	4 y	Delayed >4y			I1061T/W381X	9 y
13	F	Stillborn	Postmortem		Fetal ascites	N/A	N/A	N/A	N/A	N/A		Stillborn
14	F	Stillborn	Postmortem		Fetal ascites	N/A	N/A	N/A	N/A	N/A		Stillborn
15	F	Birth	8 y	Jaundiced LD	HS	E 17 y	8 y	13 y	5 y		I1061T/?	28 y†
16	F	Birth	2 mo	Fetal ascites LD	HS birth	E 14 y	11 y	11 y	14 y	15 y	R1059Q/?	19 y
17	F	Birth	14	Jaundiced LD	HS birth	No	No	Normal	No	No	1 bp del 2336/D874V	34 y
18	F	Birth	3 y	Jaundiced LD	HS birth	No	3 y	3 y	5 y	18 y	I1061T/N1156S	22 y
19	M	Birth	6 mo	Jaundiced LD	HS	No	No	Normal	No	No	I1061T/I1061T	2 y 2 mo
20	F	Birth	6 mo	Jaundiced LD	HS	No	No	Normal	No	No	R934Q/1 bp del 2974	1 y 11 mo
21	F	Birth	3 mo	Jaundiced	3 mo	15 y	11 y	10 y	10 y	No	F1167L/F1167L/R958Q	16 y
22	F	Birth	4 y 1 mo	Jaundiced LD	H 11 y	C 7 y E 17 y	11 y	13 y	13 y	16 y	I1061T/G992W	19 y
23	M	Birth	7 y	Jaundiced	HS	No	7 y	6 y	7 y	8 y+	I1061T/?	9 y†
24	M	Birth	11 y	Jaundiced LD	HS	No	20 y	18 y	No	No	1 bp del 2336/D874V	31 y
25	F	Birth	3 mo	Jaundiced LD	HS	No	No	Normal	No	No	I1061T/?	1 y 10 mo
26	M	Birth	2 y	Jaundiced LD		E 6 y	Yes	4 y	Yes	Yes	I1061T/?	11 y†
27	M	Birth	Birth	Severe	Yes	N/A	N/A	N/A	N/A	N/A		4 wk†
28	M	Birth	Birth	Severe	Yes	N/A	N/A	N/A	N/A	N/A		8 wk†
29	F	Birth	7 mo	Severe—still jaundiced	Yes							11 mo
30	M	Birth	1 y	Jaundiced LD		C + E 6 y		<5 y		>8 y	I1061T/?	8 y
31	F	Birth	11 mo	Jaundiced	S	No	No	Normal at 15 mo	No	No		1 y 5 mo
32	F	Birth	8 mo	Jaundiced LD	HS			Transplant 2 mo				10 y
33	M	Birth	Birth	No	No	22	Yes	12	Yes	27	I1061T/I1061T	32 y†
36	F	Jaundice at birth	4 y 5 mo	Prolonged Jaundice	HS 4 y5 mo	No	7 y	5 y 6 mo	5 y	No	I1061T/R934Q	8 y
47	M	Birth	8 mo	Prolonged Jaundice LD	Birth	C5 y 5 mo E 7 y 8 mo	5 y	5 y	5 y	9 y	I1061T/?	12 y†

Key to all tables: N/A, not applicable; S, splenomegaly; HS, hepatosplenomegaly; C, cataplexy; E, epilepsy; LD, liver disease; PJ, prolonged jaundice; PM, postmortem; y, year(s); mo, month(s); wk, week(s); †, died. Asterisks: see footnote to Table 5.

Table 2 Summary details and principal clinical signs and symptoms at and following diagnosis of patients with NPC presenting during childhood

Patient number	Sex	Age at which clinical signs were first noted	Age at diagnosis	Neonatal liver disease	Hepatosplenomegaly (HS)/ Splenomegaly (S)	Seizures	Vertical gaze palsy	Learning difficulties	Ataxia	Swallowing problems	Mutations	Age at review/ death†
35	F	4 y 7 mo	3 y 9 mo	No	No	C 6 y	6 y	4 y 7 mo	6 y	Mild 7 y	S940L/?	9 y
37**	F	9 mo	1 y	No	HS 9 mo	C5 y	5y			No	I1061T/G886R	8 y
38	F	3 y 5 mo	8 y	No	No	E 7 y C 8 y	6 y	4 y	3 y 5 mo	8 y 6 mo	1 bp del at 3591+4 (outside exon)	11 y
39**	F	5 y	6 y	No	S 5 y	No	7 y	9 y	11 y	No	I1061T/V1165M	14 y
40	F	2 y 5 mo	2 y	No	6 mo	No	3 y	2 y 5 mo	2 y 5 mo	5 y		6 y†
41**	F	4 y	4 y 9 mo	No	4 y	C 8 y E 8 y	5 y	4 y	6 y	8 y	I1061T/?	14 y†
42	F	4 y 5 mo	7 y	No	Birth	C 8 y E 10 y	5 y	4 y 5 mo	4 y	9 y	I1061T/?	16 y†
43	M	4 y	9 y	No	No	C 5 y E 5 y	6 y	4 y	6 y	10 y		15 y
44	F	4 y	8 y	No	4 y	C 5 y E 10 y	7–8 y	6 y	5 y	11 y		17 y†
45	F	7 y	10 y	No	No	C 11 y	~10 y	7 y	7 y	11 y	I1061T/?	19 y
46	F	>1 y 5 mo	4 y	No	No	C 4 y E 5 y	4 y	4 y	>1 y 5 mo	5 y	C1168Y/C1168Y	6 y 5 mo†
48	F		6 y	No	4 y	?	7 y	7 y	5 y 6 mo	4 y	Q775P/G986S	13 y†
49	M	2 y	4 y 3 mo	PJ LD	HS 3 y	C 5 y	4 y	2 y	4 y 6 mo	5 y	I1061T/?	9 y†
50	M	5 y	8 y+	PJ	No	16 y	Yes	5 y	8 y	12 y		16 y†
51	F	5 y	6 y	PJ	5 y	C 5 y E 6 y	5 y	5 y	5 y	6 y	I1061T/T1036M	9 y†
52	M	2 y 6 mo	7 y	No	S 2 y 6 mo	C 10 y	7 y	5 y	4 y 5 mo	10 y		15 y
53	M	6 y	6 y	No	S 6 y	No	No	6 y	No	No	R615L/R615L	33 y
54	F	4 y	5 y+	PJ	HS 5 y	C 5 y 5 mo	5 y	18 mo		4 y		9 y†
55*	F	2 y	8 y	No	2 y	5 y	8 y	5 y Psychiatric disturbance at 11 y	13 y	13 y	N1156S/?	21 y
56*	F	5 y	9 y	No	S 9 y	5 y	Yes	12 y		Yes	I1061T/P1007A	21 y
57	M	<2 y	Postmortem	No	No	C 2 y E 4 y		<2 y	<2 y	5 y	S940l/?	7 y†
58	M	?	2 y 5 mo	No	S ?When	No	No	No	No	No	I156S/I1061T	3 y
59	F	>4 y	10 y	No	No	C >4 y	9 y	<10 y	<10 y	No		10 y
61	F	5 y	7 y	No	No	C 8 y	7 y	5 y	7 y	8 y	I1061T/I1061T	10 y
63	M	2 y	2 y		HS <1 y 8 mo	<4 y 11 mo		<4 y 6 mo	<4 y 6 mo	<4 y 6 mo	P1007L/P1007L	5 y
64	M	?	2 y									2 y 11 mo

Table 3 Summary details and principal clinical signs and symptoms at and following diagnosis of patients with NPC presenting during adolescence

Patient number	Sex	Age at diagnosis	Age at which clinical signs were first noted	Neonatal liver disease	Hepatosplenomegaly (HS)/ Splenomegaly (S)	Seizures	Vertical gaze palsy	Learning difficulties	Ataxia	Swallowing problems	Psychiatric disturbance	Mutations	Age at review/ death†
34	M	8 y	12 y	No	S 2 y–10 y	E 11 y^{++}	10 y	10 y	8 y	18 y		I1061T/I106T	18 y
60	F	10 y	13 y	No	No	No	No	14 y	10 y	14 y		I1061T/I1061T	15 y
62	F	8 y	10 y	No	No	E 10 y	10 y	10 y	8 y	No			10 y
65	M	12 y	7 y	No	S 7 y	No	11 y	No	No	No	No	I1061T/I1061T	17 y
66	M	18 y	13 y	No	S 18 y	No	15 y	13 y	13 y^{+}	18 y	18 y	I1061T/ E1189G	21 y
67	M	16 y		Prolonged jaundice	Birth	No	No	No	No	No	No	D874V/1 bp del at 3591+4 (outside exon)	19 y
68*	F	14 y	5 y	No	No	E 13 y	14 y	5 y	13 y	13 y	12 y	N1156S/?	28 y
69	F	14 y	8 y	No	No	E 15 y	12 y	8 y^{+}	11 y	17 y	No	P1007L/?	21 y†
70	F	15 y	8 y	Prolonged jaundice	Birth	14 y	11 y	8 y	11 y	16 y	No	Y1088C/?	22y†
71	F	16 y	? birth	Prolonged Jaundice	No	No	16 y	8 y^{+}	4 y	17 y	No	I1061T/?	22 y†
72*	M	23 y	? birth	Prolonged jaundice	No	No	17 y	17 y	25 y	25 y	No	I1061T/P1007A	29 y
73	F	18 y	15 y	No	No	18 y	18 y	15 y	15 y	24 y	18 y	I1061T/P1007A	30 y†
74	M	Postmortem	? birth	Prolonged jaundice	S 2 y	No	Yes	~11 y	2 y	14 y	25 y		25 y†
75*	M	18 y	16 mo	No	S 16 mo	No	Yes	16 mo	Yes	25 y	28 y	3 bp del 1094/?	28 y†
76	F	16 y	? birth	Prolonged jaundice	No	No	16 y	11–12 y	28 y	30 y	30 y		34 y
77	M	14 y+	13 y	No	13 y	13 y+	13 y	13 y	13 y	13 y	No		29 y†
78	F	~18 y	12 y	Prolonged jaundice	No	31 y	16 y	12 y	16 y	23 y	16 y	delAG/2972–2973	40 y†
79*	F	Teens	Teens	No	No		No	Teens		Yes	23 y	I1061T/?	23 y†
81	F	16 y	25 y	No	No	C 25 y	25 y	16 y	24 y	23 y	No		30 y†

Table 4 Summary details and principal clinical signs and symptoms at and following diagnosis of patients with NPC presenting as adults

Patient number	Sex	Age at which clinical signs first noted	Age at diagnosis	Neonatal liver disease	Hepatosplenomegaly	Vertical gaze palsy	Learning/cognitive problems	Ataxia	Seizures	Psychiatric disturbance	Slurred speech	Swallowing problems	Mutations	Age at review /death†
80	M	20 y	?24	No	No		<24 y	No	No	Yes				27 y
82	M	25 y	30 y	No	No	26 y	26 y	26 y	Yes	25 y	26 y	27 y	R518W/R518W	33 y
83*	M	16 y	24 y	No	No	16 y	24 y	<24 y	No	29 y	32 y	No	I1061T/?	34 y
84*	F	11 y	24 y	No	Yes	12 y	11 y	24 y	C 24 y	32 y	24 y	30 y		35 y
85*	M	? birth	Early 20 s	Prolonged jaundice	S 4 y	Yes	11–12 y	Early 20 s	E 30 y	No				36 y
86*	M	17 y	19 y	No	S 18 y	25 y	18 y+	18 y	17 y+	17 y+	18 y	25 y		37 y
87*	F	34 y	38 y	No	No	<34 y	37 y	34 y	No	No	34 y	39 y	C419_420 ins TG	42 y
88*********	F	Teens	35 y	No	HS	Yes	Teens	35 y	No	33 y				44 y
89	F	13 y	27 y	No	No	27 y	13 y	26 y	No	No	27 y	26 y	R518W/R518W	30 y
90	F	?	49 y			?Yes	Yes						I1061T/?	51 y
91	F	25 y	25 y	No	No	No	25 y	25 y	No	No	No	No	R518W/R518W	28 y
92	M	?	27 y		Yes									30 y
93****	M	<18 y	32 y				<18 y	29 y	No	No	38 y	38 y	I1061T/?	39 y
94	M		29 y				Yes	Mild					R615C/2336 del T	34 y

whom neurological problems warranting investigation were highlighted. In retrospect, previous symptoms had existed and are therefore recorded in this table. Despite presenting in adolescence, one patient was 23 years old before diagnosis was confirmed and one patient in this age group was diagnosed after death.

Older children with NPC disease often present with learning problems during secondary schooling, although in retrospect it is often apparent that there has been a problem for longer. Histories of prolonged neonatal jaundice and psychiatric problems are common in this patient group. The clinical picture is one of survival into adulthood with slow neurodegeneration.

Adult patients with NPC

Fourteen patients (8 female, 6 male) presented and were diagnosed as adults between the ages of 19 and 49 years (Table 3b). Any symptoms tabulated before adulthood were retrospective findings based on direct questioning. Late-onset cases of NPC are characterized by insidious onset and slow progression, with cognitive and psychiatric disturbances prominent. Recent well-documented observations suggest the existence of a non-neuronopathic (or much delayed neurological onset) variant of NPC (Patterson et al 2001).

Genetics

The major *NPC1* gene has been isolated and mapped to chromosome 18q11 (Carstea et al 1997) and has a sequence homologous with that of known sterol-sensing proteins.

In patients of West European extraction a relatively common mutation in exon 21 (I1061T) of the *NPC1* gene is associated with the common juvenile- or childhood-onset form of the disease. It is also associated with the characteristic biochemical abnormality in intracellular cholesterol processing (Millat et al 1999; Pentchev et al 1985). The quoted prevalence of I1061T is about 15% (Patterson et al 2001). In this study of a possible 186 alleles, 46 have been confirmed as the common mutation, a total percentage of 25.3%. In some cases where no mutation has been found, I1061T has been excluded but not yet in all cases; this percentage may therefore be higher.

NPC1 mutations are widely spread on the gene, with one-third located in the cysteine-rich loop. With few exceptions, most mutations are private, being individual to each family (Vanier and Millat 2003).

The tables present all mutations found in the UK cohort with gaps where these have not been found. NPC2 mutation has been ruled out in this population.

Table 5 Comparisons between siblings

Patient number	Sib ships	Sex	Age at which clinical signs were first noted	Age at diagnosis	Neonatal liver disease	Hepato-splenomegaly	Vertical gaze palsy	Learning/ cognitive problems	Ataxia	Seizures	Psychiatric disturbance	Slurred speech	Swallowing problems	Mutations	Age at review/ death†
6	A	F	Birth	11 mo	Prolonged jaundice	HS	3 y	Delayed	Severe	C + E 5 y			No	T1036M/R1086H	8 y
7	A	F	Birth	11 mo	Prolonged jaundice	HS	3 y	Delayed	Severe	C+E 5 y				T1036M/R1086H	7 y†
21	B	F	Birth	3 mo	Prolonged jaundice	3 mo	11 y	10 y	10 y	15 y			No	F1167L/F1167L/R958Q	16 y
27	B	M	Birth	Birth	Severe	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A		4 wk†
28	B	M	Birth	Birth	Severe	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A		8 wk†
50	B	M	5 y	8 y+	Prolonged jaundice	No	Yes	5 y	8 y	16 y			12 y		16 y†
24*	C	M	Birth	11 y	Prolonged jaundice LD	HS	20 y	18 y	No	No			No	1 bp del 2336/D874V	32 y
17	C	F	Birth	14 y	Prolonged jaundice LD	HS birth	No	Normal	No	No			no	1 bp del 2336/D874V	34 y
30	D	M	Birth	1 y	Prolonged jaundice LD			<5 y		C + E 6 y	>8 y			I1061T/?	8 y†
26	D	M	Birth	2 y	Prolonged jaundice LD		Yes	4 y	Yes	E 6 y	Yes			I1061T/?	11 y†
34	E	M	8 y	12 y	No	S 2–10 y	10 y	10 y	8 y	E 11 y; severe			18 y	I1061T/P1007A	18 y†
72*	E	M	23 y	23 y	Prolonged jaundice	No	17 y	17 y	25 y	No	No		25 y	I1061T/P1007A	29 y
35	F	F	4 y 7 mo	3 y 9 mo	No	No	6 y	4 y	6 y	C 6 y	Mild 7 y			S940L/?	9 y
57	F	F	<2 y	Postmortem	No	No		<2 y	<2 y	C 2 y E 4 y				S940L/?	7 y†
40	G	F	2 y	No	6 mo	3 y	2 y 5 mo	2 y 5 mo	No			5 y			6 y†
52	G	M	7 y	No	S 2 y 6 mo	7 y	5 y	4 y 5 mo	C 10 y			10 y			15 y
55*	H	F	8 y	No	2 y	8 y	5 y	13 y	5 y	11 y		13 y		N1156S/?	21 y
68*	H	F	14 y	No	No	14 y	5 y	13 y	E 13 y	12 y		13 y		N1156S/?	28 y
79	I	F	Teens	No	No	No	Teens			23 y		Yes		I1061T/?	23 y†
83*	I	M	24 y	No	No	16 y	24 y	>24 y	No	29 y		No		I1061T/?	34 y
86	J	M	19 y	No	S 18 y	25 y	>18 y	18 y	17 y+	17 y+		25 y		3 bp del 1094/?	37 y
75*	J	M	18 y	No	S 16 mo	Yes	16 mo	Yes	No	28 y		25 y		3 bp del 1094/?	28 y†
82	K	M	30 y	No	No	26 y	26 y	26 y	Yes	25 y		27 y		R518W/R518W	33 y
89	K	F	27 y	No	No	27 y	13 y	26 y	No	No		26 y		R518W/R518W	30 y
91	K	F	25 y	No	No	No	25 y	25 y	No	No	No	No		R518W/R518W	28 y
13	L	F	PM		Fetal ascities	N/A	N/A	N/A	N/A	N/A	N/A	N/A			Stillborn
14	L	F	PM		Fetal ascities	N/A	N/A	N/A	N/A	N/A	N/A	N/A			Stillborn

It is of note that 12 sets of siblings were identified. The disease manifestations and progression in these individuals were relatively different in 9 of them. Only 2 sets followed a very similar pattern of manifestation, progression and outcome, including siblings who were stillborn.

Data included in other papers: *Niemann–Pick Disease type C in adults (Imrie et al 2002). **Isolated splenomegaly as the presenting feature of Niemann–Pick disease type C (Imrie et al 2001). ***Identification of novel mutations in the NCP1 gene in German Patients with Niemann–Pick disease. (Kaminski et al 2002) and (Grau et al 1997). ****Treatment with miglustat reverses the lipid-trafficking defect in Niemann–Pick disease type C. (Lachmann et al 2004). *****Niemann–Pick mimicking features of multiple sclerosis (Grau et al 1997).

Discussion

Niemann–Pick disease is clinically heterogeneous with a wide age range at presentation. It is a rare autosomal recessive disorder with an estimated birth incidence of 1:150 000 (Patterson et al 2001), and between 1990 and 1999 the detection rate of new cases in the UK was 4–5 patients per year. Understanding the natural history of NPC disease is important in anticipating the future palliative care needs of these patients and their families and in assessing the long-term effects of potential interventions.

Presenting features are variable in all age groups, although there are common features and the overall progression of the disease is similar. Prolonged neonatal jaundice is a feature in all age groups and investigations to exclude NPC are usually part of the normal practice in liver disease/neonatal units in patients who present in this way in the UK. Many of the patients in this review underwent intensive liver investigations, including surgery, in the neonatal period, only for NPC to be diagnosed when neurological signs had appeared, sometimes many years later. The degree of neonatal liver disease is not, however, an indicator of the severity of disease progression, as illustrated by those adults who have minimal symptoms despite a neonatal presentation with liver disease.

It is important to remember this when counselling a family in whom a diagnosis of NPC was established in the neonatal period following investigations of prolonged jaundice. In addition, the presence of splenomegaly is a more consistent feature than hepatomegaly in neonates, and this alone may lead to early diagnosis in such patients. With this in mind, we have established a clinic for young children who have been diagnosed in the early years of life but who have no symptoms, to provide family support and counselling. The adolescent and adult presentation groups comprise 30 patients with 20 surviving, some into the 3rd, 4th and 5th decades. This emphasizes the fact that NPC is not only a disease of childhood but should be considered in adults who present with progressive neurological or intellectual decline (Trendleburg et al 2006). Table 4 highlights that in some families phenotypic differences exist even between genetically similar siblings. In some female patients the disease presented in or was apparently exacerbated by pregnancy. It is known that, *in vitro*, progesterone strongly blocks LDL-induced cholesterol ester synthesis and the metabolic precursor of progesterone, pregnenolone, induces extensive accumulation of cholesterol in lysosomes (Butler et al 1992); therefore the hormonal effects that occur during pregnancy may account for the exacerbation of the disease during gestation. In contrast, data from the NPC mice showed delayed progression and deterioration (Griffin et al 2004). Further study is required to clarify this conflict but it is likely that the main cause of deterioration seen in some pregnancies is that the pregnancy itself may lead to an increase in metabolic 'stress' in affected patients

There is currently no effective treatment for NPC apart from symptom control and palliative care. Lipid-lowering drugs (Erickson et al 2000; Patterson et al 1993) and bone marrow transplantation (Hsu et al 1999) have been ineffective in halting progression.

Substrate reduction therapy (SRT) using Miglustat (Zavesca, Actelion) has proved effective in Gaucher disease (Cox et al 2003; Elstein et al 2004). In NPC where there is similar accumulation of glycosphingolipids, a similar approach might prove to be effective. Recent abstracts have demonstrated encouraging early results in NPC patients with this product (Patterson et al 2005).

Demonstration of improved endosomal uptake and normalization of lipid trafficking in the peripheral blood B lymphocytes of a patient treated with miglustat provides some additional support for this therapeutic rationale (Lachmann et al 2004).

Conclusion

The results of this study demonstrate that NPC can present at all ages and that early observation of symptoms is not always an indicator of possible disease progression. This is important when discussing prognosis and future reproductive history for families as it may affect decision making.

With a more accurate understanding of the natural history of NPC it is possible to produce individualized care plans for patients, mobilizing the full range of available community services. Greater knowledge of the clinical course of the disease will be of vital importance as more treatments are developed in an attempt to treat the disorder.

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