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Natural course of Fabry disease: changing pattern of causes of death in FOS – the Fabry Outcome Survey

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ABSTRACT

Background

Fabry disease is a rare X-linked lysosomal storage disorder characterized by severe multisystemic involvement that leads to major organ failure and premature death in affected men and women. Over the past 7 years, the Fabry Outcome Survey (FOS) has collected data on the natural history of Fabry disease and the long-term efficacy and safety of enzyme replacement therapy. This paper provides an update since the first analysis of FOS data.

Design

Baseline data on clinical manifestations and causes of death in a cohort of 1453 patients (699 males) from 19 countries worldwide were analysed. Causes of death of affected relatives were analysed separately.

Results

The most frequently reported signs and symptoms of Fabry disease were neurological. Cardiac, ocular, gastrointestinal, dermatological, auditory and renal manifestations were also common. The principal causes of death among 181 affected relatives of patients in FOS (the majority of whom had died before 2001) were renal failure in males (42%) and cerebrovascular disease in females (25%). In contrast, among the 42 patients enrolled in FOS whose deaths were reported between 2001 and 2007, cardiac disease was the main cause of death in both males (34%) and females (57%).

Conclusion

These data suggest that the importance of renal disease as a cause of death in patients with Fabry disease is decreasing, while the importance of cardiac disease is increasing. This pattern likely reflects improvements in the management of renal disease in patients with Fabry disease.

INTRODUCTION

Fabry disease is a rare X-linked lysosomal storage disorder due to deficient activity of the enzyme α -galactosidase A. It is characterized by severe multisystemic involvement that ultimately leads to major organ failure and premature death in affected men and women [1]. The condition has conventionally been considered to be rare, affecting only 1 in 40,000–117,000 live male births [1, 2]. However, a recent screening study suggested a much higher incidence of 1 in 3100–4600 individuals [3].

α -Galactosidase A deficiency is caused by a number of mutations affecting the *GLA* gene, many of which are private (i.e. occurring in only single or small numbers of families) [4]. As a result of α -galactosidase A deficiency, there is progressive accumulation of undegraded glycosphingolipids, predominantly globotriaosylceramide (Gb₃), within cell lysosomes throughout the body. Common clinical features of Fabry disease include acroparaesthesia and pain crises, gastrointestinal symptoms, angiokeratomas and corneal dystrophy.

Despite the fact that Fabry disease follows an X-linked pattern of inheritance, it is now widely accepted that female heterozygotes can be severely affected, although progression of the disease to organ failure generally occurs later in life and symptom severity tends to be milder and more variable than in males [5–7]. Renal failure has been found to be a frequent cause of death in several studies, particularly in males [5, 8, 9]. In females, data on small patient groups suggest that cardiac disease and cerebrovascular disease are the most frequent causes of death [5, 9, 10, 11]. Death occurs on average 15 years earlier in females and 20 years earlier in males compared with the general population [6, 10, 12].

Enzyme replacement therapy (ERT) has become an established treatment for Fabry disease following demonstrations of both efficacy and safety in adults and children [13–16]. Treatment guidelines concerning ERT have now been published [17]. Early diagnosis of Fabry disease is therefore important, and clinicians in a range of specialties, as well as general practitioners, should be aware of the signs, symptoms and natural history of the disease.

This paper provides an update of the demographic and baseline clinical characteristics of a large cohort of patients with Fabry disease enrolled in FOS – the Fabry Outcome Survey – and examines the causes of death among patients and their affected relatives [5].

METHODS

Patients and data collection

FOS has been approved by the Ethics Institution Review Boards of participating centres (Appendix A), and all patients gave written informed consent. To minimize bias, data from all consenting patients are entered. All patients enrolled in FOS are receiving, or are candidates for, ERT with agalsidase alfa. On enrolment, each patient's medical history is documented by a physician or nurse specialist, including the year of diagnosis of Fabry disease, signs and symptoms of the disease, treatment, demographic details and family history. All measurements performed routinely in clinical practice are entered into the database. Assessments of cardiac and renal function, ophthalmological, gastrointestinal and audiological examinations are optional. Anonymized data are submitted electronically by participating physicians to

the central FOS database. Disease severity is systematically categorized in all patients using an adapted version of the Mainz Severity Scoring Index (FOS-MSSI) [18].

Data analysis

Student's two-sample and one-sample *t*-tests and Fisher's exact/Chi-square tests were used for statistical analyses, using SAS version 9.1 (Cary, NC). Values are presented as mean (SD) unless otherwise stated; $p < 0.05$ was considered significant.

RESULTS

Patient demographics

Table 1 shows the baseline characteristics of the 1453 patients (699 males) enrolled in FOS at the time of this analysis (December 2007). The majority were Caucasian (95.7%).

Disease severity

The severity of Fabry disease was greater in males than in females in FOS, as indicated by the FOS-MSSI total score [16.9 (10.8) vs. 11.0 (9.0), respectively; $p < 0.001$]. This was true for all four subcategories of the FOS-MSSI score (general, neurological, cardiovascular and renal).

Table 1. Mean baseline characteristics of the 1453 patients with Fabry disease in the Fabry Outcome Survey.

	Males	Females
Total patient population	n = 699	n = 754
Age at entry into FOS (years)	34.2 ± 15.4	37.9 ± 17.9*
Age at diagnosis (years)	23.5 ± 15.4	30.8 ± 17.6*
Weight at entry (kg)	66.3 ± 19.5	64.2 ± 17.8
Age at start of ERT (years)	41.5 ± 17.0	33.8 ± 14.1
Adults	n = 581	n = 620
Age at entry into FOS (years)	38.9 ± 12.3	43.6 ± 14.4
Number receiving ERT	n = 447	n = 310
Age at treatment start (years)	37.2 ± 11.8	45.8 ± 13.8
Children	n = 118	n = 134
Age at entry into FOS (years)	11.2 ± 4.4	11.7 ± 4.6
Number receiving ERT	n = 70	n = 48
Age at treatment start (years)	11.8 ± 4.3	13.7 ± 4.2

* $p < 0.001$ compared with males.

Signs and symptoms in male and female patients

The prevalence and age at onset of the main signs and symptoms of Fabry disease in males and females at entry into FOS are shown in Table 2. As in the previous analysis of FOS data, the most frequently reported signs and symptoms of Fabry disease were neurological, affecting 75% of males and 61% of females (Table 2). Cardiac, ocular, gastrointestinal, dermatological, auditory and renal manifestations were also common.

Renal signs and symptoms of Fabry disease were reported in 693 patients in FOS.

Proteinuria was the most common renal manifestation, being observed in 332 males and 246 females. Renal failure was present in 134 males and 21 females. In total, 89 males and five females had end-stage renal disease (ESRD) [mean age of onset, 32.3 (19.7) and 23.3 (21.3) years, respectively].

Cardiac manifestations were recorded in 422 male and 376 female patients. Of these patients, 284 males and 180 females had left ventricular hypertrophy (LVH), which was reported to have begun at 28.7 (19.3) and 34.1 (24.9) years of age, respectively.

Cerebrovascular events occurred with approximately the same frequency in males and females [25% (n = 172) and 21% (n = 159), respectively]. Stroke was reported in 39 females and 63 males [mean age of onset, 51.4 (14.1) and 39.2 (11.5), respectively].

TIA was recorded in 46 females and 60 males [mean age of onset, 46.6 (14.8) and 38.4 (13.6), respectively].

Table 2. Prevalence and age at onset of organ system involvement in patients with Fabry disease enrolled in the Fabry Outcome Survey.

Organ system	Males (n = 699)		Females (n = 754)		Total (n = 1453)	
	Percentage with signs/ symptoms	Mean age at onset (years)	Percentage with signs/ symptoms	Mean age at onset (years)	Percentage with signs/ symptoms	Mean age at onset (years)
Neurological	75	15.1 (15.0)	61	20.9 (17.9)	68	17.9 (16.6)
Cardiac	60	29.2 (14.4)	50	34.5 (17.6)	55	31.6 (16.1)
Ocular	58	29.2 (15.1)	49	31.9 (18.3)	53	30.5 (16.8)
Gastrointestinal	57	22.2 (16.1)	45	26.8 (19.2)	51	24.3 (17.7)
Dermatological	66	20.0 (15.4)	37	30.8 (19.0)	51	24.3 (17.7)
General	59	18.7 (15.9)	44	26.1 (19.0)	51	21.8 (17.7)
Auditory	56	29.0 (15.3)	44	33.3 (19.1)	50	31.0 (17.2)
Renal	59	32.6 (12.7)	38	38.5 (16.2)	48	35.0 (14.5)
Musculo-skeletal	39	26.9 (16.8)	34	34.7 (18.4)	36	30.5 (17.9)
Vascular	35	34.5 (12.9)	25	41.7 (16.4)	30	37.4 (14.9)
Psychiatric	27	32.4 (15.3)	23	36.5 (17.0)	25	34.4 (16.2)
Respiratory	29	32.9 (17.3)	21	36.3 (20.5)	24	34.3 (18.7)
Cerebrovascular	25	31.3 (15.2)	21	36.4 (18.1)	23	33.7 (16.8)
Endocrinological	5	31.4 (20.4)	8	42.1 (17.9)	7	39.0 (19.1)
Genital	6	35.0 (17.9)	1	38.6 (16.7)	4	35.7 (17.5)

Mortality

Deaths in patients in FOS

Data on age and cause of death in patients who have received ERT at any point in time has been collected in FOS since 2001. More recently (since August 2006) data has been collected on deaths in patients who had never received ERT. Information on any death can be entered retrospectively. At the time of this analysis, age and cause of death had been reported for 42 patients (35 male, 7 female) in FOS (Table 3). Mean age at death was 51.8 (9.3) years and 64.4 (10.0) years for males and females, respectively. The primary cause of death in both male and female patients was cardiac disease, reported in 34% (n = 12) and 57% (n = 4) of cases, respectively. Of the 42 patients who died, 33 (28 males) had received ERT at some point whilst alive: and among them cardiac disease remained the most common cause of death (n = 12; 36%), followed by infection (n = 5; 15%) and multisystemic disease (n = 4; 12%). Renal failure was responsible for three deaths (n = 3; 9%). Cardiac disease was also the most common cause of death (n = 4 of 9; 44%) among patients who died but had not received ERT at any point. However, data on deaths in patients not receiving ERT have only been collected since August 2006, and therefore the untreated group is not entirely representative of all untreated patients.

Table 3. Cause of death in affected male and female patients in the Fabry Outcome Survey. Data on patients who had received ERT at some point prior to death were available during the period between 2001 and 2007. Information on deaths of patients who never received ERT could be added from August 2006 onwards.

Cause of death	Received ERT at some time			Never received ERT			Overall		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Cardiac	10	2	12	2	2	4	12	4	16
Renal	3	0	3	0	0	0	3	0	3
Cerebrovascular	3	0	3	1	0	1	4	0	4
Respiratory	2	0	2	1	0	1	3	0	3
Malignancy	1	1	2	1	0	1	2	1	3
Infection	5	0	5	0	0	0	5	0	5
Multisystemic	2	2	4	2	0	2	4	2	6
Other	2	0	2	0	0	0	2	0	2
Total	28	5	33	7	2	9	35	7	42

The 42 patients in FOS who died were severely affected by Fabry disease. From the available absolute data shown in Table 4, both men and women who died had higher MSSSI scores than patients who were alive. Data were also available on whether patients had specific manifestations either before or at/after the start of ERT

5 (information recorded as yes/no only). Among the 42 deceased patients, LVH was reported in 29 cases (25 male, 4 female). LVH was present before the start of treatment in all 22 of the patients who went on to receive ERT and in 7 of the 9 patients who never received ERT. Absolute data on left ventricular mass (LVM) were available for 19 of the 42 patients and show that mean LVM at FOS entry was higher
10 in patients who died relative to patients who were still alive (Table 4). Conduction abnormalities were evident in 19 patients (15 male, 4 female), 15 of whom received ERT, and were present prior to the commencement of ERT in 11 (9 male) of these 15 patients. Valvular disease was recorded in 16 patients (13 male): in three males this was recorded after the start of treatment only.

15

Proteinuria was recorded as present at some point in time (yes/no) in 27 of the 42 patients (21 male, 6 female). Among the 22 patients in this group who received ERT, proteinuria was present prior to the commencement of ERT in 17 patients (13 males).

Absolute data were available for 23 patients showing higher proteinuria levels in
20 patients who died than in those who were alive (Table 4). Mean proteinuria levels based on the values available were higher in patients who received ERT [females (n=4), 1521.9 mg/ 24 hrs (range, 52.5–2495.0); males (n = 17), 900.4 mg/ 24 hrs (range, 21.0–3955.0)] than in those who did not [females (n=1), 250.0 mg/ 24 hrs; males (n = 1), 970.0 mg/ 24 hrs]. Hypertension was reported in 20 (15 male) of the
25 patients who died. Sixteen of these patients are known to have received ERT and in

15 cases (12 male) hypertension was present prior to the commencement of ERT. In patients who received ERT at some point, haemodialysis was reported prior to the commencement in 4 males, peritoneal dialysis in 2 males and renal transplantation in 7 males. After the start of ERT, one further male patient started haemodialysis and 5
5 underwent renal transplantation. Among deceased patients who never received ERT, 2 males were on haemodialysis.

Stroke was reported in 19 of the 42 patients who died (16 male, 3 female) and TIAs in 13 patients (11 male). Of the 14 stroke patients who had received ERT, 10 (9 male)
10 experienced strokes both before and after commencement of ERT. Two males had no further strokes after the commencement of ERT, while 2 males suffered their first stroke at/after the start of ERT. The remaining patients either did not receive ERT (3 male, 2 female) or reported stroke only prior to the start of treatment (2 male).

15 Chronic pain was reported in 25 (21 male), and asthma in 14 (10 male) of the 42 patients who died.

Table 4. Mean (SD) data at FOS entry according to whether patients were alive or dead at the time of the analysis.

	Adult females		Adult males	
	Alive	Dead	Alive	Dead
Proteinuria (mg/24h)	324.5 (528.4), n = 311	1267.5 (1106.0), n = 5	641.6 (967.9), n = 301	904.3 (1127.5), n = 18
Serum creatinine (mg/dL)	0.9 (0.4), n = 424	1.2 (0.3), n = 7	1.6 (1.7), n = 388	2.3 (2.3), n = 25
Estimated GFR (mL/min/1.73m ²)	80.6 (21.9), n = 342	54.2 (15.1), n = 7	80.5 (37.0), n = 335	72.0 (49.4), n = 22
Midwall fractional shortening (%)	16.8 (3.4), n = 204	11.8 (4.4), n = 6	15.4 (4.5), n = 132	13.8 (3.6), n = 10
LVM (g)	46.9 (20.1), n = 218	86.1 (29.0), n = 6	54.6 (21.7), n = 153	82.1 (38.8), n = 13
MSSI	11.8 (9.0), n = 558	26.4 (14.5), n = 7	17.9 (10.1), n = 497	30.7 (12.1), n = 33
Age at FOS entry (years)	43.4 (14.3), n = 613	61.0 (10.0), n = 7	38.2 (12.1), n = 546	49.8 (9.6), n = 35
Age at death (years)	–	64.4 (10.0), n = 7	–	51.8 (9.3), n = 35

GFR, glomerular filtration rate; LVM, left ventricular mass; MSSI, Mainz Severity Score Index.

Deaths in affected relatives of patients in FOS

Information was available on the cause of death in 181 affected relatives (118 males) of patients in FOS (Table 5). Precise data on the year of death were not available; however, the majority of these deaths occurred before ERT became available in 2001.

- 5 The most common causes of death in affected male family members were renal failure (n = 50; 58% aged 21–50 years) and cardiac disease (n = 31; 71% aged 21–50 years). The cause of death was unknown in 16 male relatives, but Fabry disease-related causes were suspected. Affected female relatives tended to live longer than affected male relatives. The commonest causes of death in female relatives were
- 10 cerebrovascular disease (n = 16; 38% aged 21–50 years, 50% aged >50 years), followed by cardiac disease (n = 12; 92% aged >50 years) and malignancy (n = 10). Seven female relatives died as a result of renal disease. Cause of death was unknown, but the family member was known or suspected to have suffered from Fabry disease, in 16 cases.

15

20

Table 5. Number of deaths in relatives of patients enrolled in the Fabry Outcome Survey reported up to December 2007. Data are shown according to reported age at death.

Cause of death	Number of deaths in male relatives					Number of deaths in female relatives					Overall number of deaths				
	Age at death (years)					Age at death (years)					Age at death (years)				
	0–20	21–50	>50	Unknown	Total	0–20	21–50	>50	Unknown	Total	0–20	21–50	>50	Unknown	Total
Cardiac	0	22	8	1	31	0	1	11	0	12	0	23	19	1	43
Renal	0	29	14	7	50	0	5	2	0	7	0	34	16	7	57
Cerebrovascular	0	5	5	2	12	0	6	8	2	16	0	11	13	4	28
Respiratory	0	0	1	0	1	0	0	0	0	0	0	0	1	0	1
Malignancy	0	2	1	0	3	0	4	5	1	10	0	6	6	1	13
Infection	0	3	0	2	5	0	0	1	0	1	0	3	1	2	6
Multisystemic	0	0	0	0	0	0	0	1	0	1	0	0	1	0	1
Other	0	7	3	6	16	0	4	5	7	16	0	11	8	13	32
Total	0	68	32	18	118	0	20	33	10	63	0	88	65	28	181

DISCUSSION

This report describes the baseline clinical manifestations of Fabry disease in a large cohort of patients from 19 countries worldwide enrolled in the FOS database. The number of patients enrolled in FOS has increased steadily over time since the first
5 report in 2004 [5]. The present analysis confirmed that the major clinical manifestations of this multisystemic disease in early adulthood were pain (acroparaesthesia), angiokeratoma and renal, cardiac and cerebrovascular disease. Gastrointestinal manifestations and sensory organ abnormalities were also common. Although some signs and symptoms including pain and gastrointestinal disturbances
10 were evident from an early age, end-stage organ damage was not seen in children in FOS.

Analysis of data on causes of death among patients currently in FOS and among their relatives, suggests that the clinical course of Fabry disease may be changing.
15 Consistent with previously published historical data [12], renal failure was the most common cause of death in affected relatives of patients in FOS (31%), the majority of whom had died prior to 2001. When analysed according to sex, renal failure was the major cause of death in affected male relatives (42%) and cerebrovascular disease was the most frequently reported cause of death in affected female relatives (25%), as has
20 been reported previously. Cardiac disease was the second most important cause of death in both affected male and affected female relatives.

Data obtained for patients enrolled in FOS whose deaths were reported between 2001 and 2007 are somewhat different. In these 42 patients, cardiac disease was the most
25 frequent cause of death in both males (34%) and females (57%). Only three patients

died from renal disease (7%). These data suggest that deaths from renal failure are becoming less frequent over time and the majority of patients are now dying from cardiac disease. This was true irrespective of whether or not patients had received ERT, although formal comparison of deaths in ERT-treated and non-ERT-treated
5 patients was not possible because of the limited data available from the latter group.

A recent retrospective review of 447 patients (279 male, 168 female) with Fabry disease [19] confirms that Fabry nephropathy has a higher prevalence, occurs earlier and progresses more rapidly in the absence of ERT among males than females. This
10 study also found a high prevalence of cardiac events (mainly arrhythmias) in 49% of males (35% females) prior to commencement of ERT; strokes/TIAs occurred in 11 and 6% of males and, 8 and 4% of females, respectively.

Evidence from our own study suggests that cardiac involvement was well established
15 in many of the patients who died. LVH was present in almost 70% of those enrolled in FOS who died, and was present in 7 of the 9 patients who died without receiving ERT. Increased LVM, valvular heart disease, conduction disturbances and hypertension were also present prior to commencement of ERT in most of the deceased patients. It seems likely therefore that the majority of deaths attributed to
20 cardiac causes resulted from the progression of pre-existing cardiac involvement associated with Fabry disease. However, a proportion of these cardiac deaths may be unrelated to Fabry disease, as cardiovascular disease is a major cause of death in normal adults, accounting for nearly half of all deaths in Europe (48%) [20]. In addition, the majority of the patients who died from cardiac-related causes also had
25 severe manifestations affecting other organ systems (primarily renal and CNS).

In the context that there is a high prevalence of renal disease, including ESRD, among patients currently in FOS, the few deaths associated with renal failure is striking.

Improvements in supportive care, greater access to dialysis facilities and improved

5 management of hypertension may all contribute to the lower number of deaths due to renal disease. Although ERT has not been shown to be effective in reversing ESRD, several studies confirm that both agalsidase alfa and agalsidase beta can slow the decline, or perhaps even stabilize, renal function in patients with lesser degrees of renal impairment [21–24]. Current guidelines for the treatment of Fabry disease
10 emphasize the importance of angiotensin-converting enzyme inhibitors/angiotensin receptor blockade, careful management of hypertension and early initiation of ERT [25]. As cardiac disease is now the most commonly reported cause of death, its treatment is clearly important. Studies have shown that both agalsidase alfa and beta improve cardiac structure and function in males and females with Fabry disease [26–
15 29]. If treatment of cardiac and renal dysfunction are optimized and patients receive optimal supportive care, it is also conceivable that early stroke may be prevented, although recent reports suggest that premature stroke may still occur in patients receiving ERT [30]. Unfortunately, due to the lack of an appropriate control group, it was not possible to evaluate specifically whether ERT changed the progression of
20 disease manifestations or increased the life expectancy of patients with Fabry disease in the present study.

As is generally the case for most non-interventional observational databases, there are several limitations to this study. First, as all clinical decisions and data entry are at the

25 discretion of the attending physician, data sets are often incomplete and there is a lack

of standardization in the assessments conducted between patients. There is also variability between patients in terms of the treatment protocols used and the supportive care provided. Thirdly, patient-reported data on the causes of death in relatives are subject to selective recall and these data have not been verified with
5 reference to source documents. In addition, only simple data are available for some variables, such as cause of death. Finally, the nature of the database makes it likely that untreated and mildly affected patients are under reported.

In conclusion, these data suggest that the natural clinical course of Fabry disease may
10 be changing. The importance of renal failure as a cause of death is decreasing, while the importance of cardiac disease is increasing. This is partly a result of significant improvements in supportive care, particularly for renal failure and hypertension, which have occurred in recent years. Such improvements, in addition to the provision of ERT, may be contributing to changes in morbidity and mortality associated with
15 Fabry disease. In future, it is hoped that these natural history data will enable the accurate assessment of the impact of ERT in patients with Fabry disease. There remains, however, a very real need for new treatments, particularly for oral therapies and for the development of treatment approaches that are better able to access the CNS and organs such as the heart and kidney.

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APPENDIX A

Ethics committee approval

The FOS database has been approved by the Ethics Institution Review Boards of the over 100 participating centres, and all patients gave written informed consent. As so

- 5 many investigators and participating centres are involved in FOS, we have provided a list of the investigators who submitted data to FOS (correct as of December 2007), together with their location:

Argentina: P. Rozenfeld (La Plata).

Australia: K. Nicholls (Melbourne).

- 10 **Austria:** G. Sunder-Plassmann, J. Kleinert, A-C. Hauser, O. Bodamer, W. Kristoferitsch, W. Schreiber (Vienna); B. Plecko, T. Kroepfl, I.P. Kotanko, C. Binder, M. Brunner-Krainz (Graz). Belgium: C. Verellen-Dumoulin, F. Dehout, D. Roland, F. Henry, J. Jaumotte (Charleroi); F. Eyskens, A. Neirinck (Antwerp); M.C. Nassogne, Y. Pirson, A. Ballaut, P. Goyens, M. Libert (Brussels); N. Mazoin (Verviers).
- 15 **Brazil:** R. Giugliani, L. Kalakun, C. Netto, T. Vieira, L. Jardim (Porto Alegre). **Canada:** B. Lemieux (Sherbrooke); D. Bichet, M.F. Arthus, C. Fortier (Montreal); J. Clarke, C. Azcona (Toronto); M. West, K. LeMoine (Halifax); A. Chan, E. Kowal-Zuk (Edmonton); L. Clarke (Vancouver).
- Czech Republic:** A. Linhart, L. Golánv , J. Bultas, J-C. Lubanda, S. Magage, D. Karetová, G. Dostalova.
- 20 **France:** G. Choukroun (Amiens); J. Berthelot (Angers); S. Carey Reomonney (Besançon); D. Lacombe (Bordeaux); S. Benziane (Cambrai); A. Khau van Kien (Montpellier); J.M. Mittelberger (Freyming Merlebach); C. Thevenot (Laon); E. Hachulla, D. Dobbelaere (Lille); B. Dussol (Marseille); R. Reade (Maubeuge); P. Kaminsky (Nancy); C. Guyot, M. Lino (Nantes); T. Ghafari (Nice); E. Monlun (Pau); D.P. Germain, N. Ouali, G. Touati, O. Lidove, B. Knebelmann (Paris); R. Perrichot (Vannes); R. Jaussaud (Reims); B. Richalet (Saint Lô); V. Klotz (Selestat); E. Andres (Strasbourg); D. Caraman (Thionville); J. Bazex (Toulouse); P. Hardy (Arras); P. Bataille (Boulogne/mer).
- 25 **Germany:** M. Beck, K. Baron, S. Delgado-Sanchez, R. Hartung, G. Kalkum, C. Whybra, C. Kampmann, C. Wiethoff, A. Schwarting, A. Keilmann, S. Pitz, K. Bruns, F. Bähner, K. Lackner (Mainz); B. Koletzko, B. Hoffmann, B. Pontz (Munich); H.P.H. Neumann, M. Cybulla, G. Schlueh, A. Winter (Freiburg); A. Das, S. Illsinger, T. Lücke (Hannover); A. von Arnim-Baas, J. Hennermann, N. Weinhold, J-M. Berger
- 35 (Berlin); S. Stolz (Cottbus); S. Grabbe, T. Jansen, E. Chrobot (Essen); A. Gal, E. Schäfer, K. Ullrich, N. Muschol, I. Berkau (Hamburg); A. Rolfs, T. Böttcher, S. Miethe, F. Rimmele (Rostock); C. Wanner, I. Davydenko, R. Wössner (Würzburg); S. Al Sawaf, B. Hoffmann (Düsseldorf); R. Schueuermann (Mannheim); C. Haase (Jena).
- 40 **Hungary:** L. Maródi (Debrecen). **Italy:** O. Gabrielli (Ancona); D. Concolino (Catanzano); W. Borsini (Firenze); R. Parini, S. Sala, M. Rigoldi (Monza); R. Di Vito (Ortona); A.P. Burlina, A. Burlina

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5 **Norway:** G. Houge (Bergen); Ø. Kaarbøe (Ålesund).

Slovenia: B. Vujkovic (Slovenj Gradec).

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20 **USA:** E. Boyd, K. Crandall (Asheville); G. Pastores, N. Barnett (New York); R. Schiffmann, M. Ashmus (NIH); H. Lien, M. Van Skiver (Arizona); R. Martin

25 (Washington).

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35