brief report

Infantile onset Pompe disease: A report of physician narratives from an epidemiologic study

Deborah Marsden, MBBS

Purpose: To review the narratives that detailed the most important features of Infantile Onset Pompe disease (IOPD) from the physician's perspective, submitted as part of a large multicenter, multinational epidemiologic natural history study. **Methods:** Inclusion in the epidemiologic study required documentation of onset of symptoms in the first 12 months of age and GAA enzyme deficiency or GAA mutation(s). In all, 300 cases were screened; 168 cases from 33 study sites in 9 countries met all eligibility criteria. In addition, 125 narratives that summarized the most important clinical features of IOPD, reflecting the opinion of the participating physicians who had provided access to the records for the independent review, were analyzed and are reported separately. A total of 98 variables were analyzed. **Results:** Hypotonia was the most common presenting symptom, occurring in 75% of patients; muscle weakness was a presenting symptom in 59% of patients. The most frequent sign noted on physical examination was hypotonia (82%); respiratory distress, cardiomegaly, weakness, and cardiac failure were also frequent. Progression of disease was characterized by increased respiratory distress (72%), hypotonia (66%), and cardiac failure (58%). The most frequent supportive treatments were cardiac medications (52%) and oxygen supplementation (35%). Little psychosocial information was included. **Conclusion:** Physician narratives provide a unique perspective on the natural history of IOPD and are useful adjuncts to other data collection. Overall, there was concordance with the data obtained by the independent abstractors. ***Genet Med* 2005:7(2):147–150.**

Key Words: *Pompe disease, infantile onset, narratives, natural history.*

Pompe Disease is a rare autosomal recessive disorder of glycogen metabolism due to a deficiency of acid α-glucosidase, characterized by intralysosmal storage of glycogen. The overall worldwide incidence of infantile onset Pompe disease is 1/100,000 to 1/200,000 with variation in different populations. It can be as frequent as 1/14,000 in the African American population.[1] Symptoms in the classic infantile onset form of the disease (IOPD) can be recognized as early as the neonatal period with evidence of cardiac dysfunction, although typically there is evidence of rapidly progressive hypotonia, weakness, cardiomyopathy, and respiratory insufficiency. A later onset, less rapidly progressive variant, presents more commonly with myopathy that may evolve into respiratory insufficiency in adolescence or adulthood.

The initial presentation of IOPD is usually at about 4 months of age. The diagnosis is usually made by 6 months of age and death typically occurs by 1 year of age, primarily due to cardiorespiratory failure.[2] Until recently, there was very little published information on the natural history of this disease or the psychosocial impact of the disease on families. A large multinational epidemiologic study was recently undertaken to document the presentation and progression of infantile onset Pompe disease as assessed by an independent but uniform set of variables. Epidemiologic studies are not generally designed to collect subjective data, but in this study, it was also considered important to obtain nonobjective opinions of the physicians who cared for these infants, reflecting what they, based on their own experience, considered to be the most significant features of the onset of the symptoms, progression of the disease, and psychosocial impact on the families. It was felt that these physicians might provide a different perspective on this disease, compared to the independent abstractors, who collect data without any clinical bias.

METHODS

Physicians who care for patients with Pompe disease were contacted and asked to participate in the natural history study by providing access to the medical records of patients who had been assessed at that center. Records could be of patients with whom the physician had had direct contact, either for direct diagnosis and management or as a consultant, or ascertained by review of medical records identified from institutional databases. Charts dated from 1969 to 2002. In all, 300 cases were screened; 168 cases from 33 study sites in nine countries met all eligibility criteria. A trained abstractor reviewed each record

From the Division of Genetics and Metabolism, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts.

Deborah Marsden, Division of Genetics and Metabolism, Children's Hospital Boston, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115.

Received: July 16, 2004.

Accepted: November 24, 2005.

DOI: 10.1097/01.GIM.0000154301.76619.5C

and collected uniform data from each eligible chart. These results are reported elsewhere.[3] The individual physicians who provided access to charts were also asked to submit a narrative report of what they personally considered to be the most pertinent features of the disease and the progression of physical findings, either from their own recollection of the patient, or from their impressions of the information documented in the patient's chart. The physicians did not have access to the data collected by the abstractors and were not aware of the specific information being collected. Not all physicians who provided access to the abstractors submitted narrative reports.

Inclusion criteria for the natural history study were onset of symptoms of Pompe disease before 1 year of age and proven enzyme diagnosis of alpha glucosidase deficiency. Data were collected from multiple sites in North America, Europe (UK, France Austria, Germany, and Italy), the Middle East (Israel) and Asia (Taiwan). Institutional Review Board approval was obtained if required by the individual institutions. The 125 physician narrative reports were analyzed independently from the natural history study for this report. Data were tabulated for 98 variables, including family history of Pompe disease, birth history, symptoms at presentation, physical exam, progression of symptoms, diagnostic evaluation, and supportive treatment. The responding physicians were also asked to comment on family reactions to the disease, as documented in the chart.

RESULTS

Several reports were based on both direct recollection of the patient with confirmation by chart review. The majority, however, were based solely on chart review by the participating physician. Only eight of the physicians were the primary treating physician. Many patients were only seen on one occasion, usually for formal confirmation of an already suspected diagnosis of Pompe disease, and in 23 (18%) cases because of a positive family history. Narratives noted consanguinity in 21 (17%) families, mostly from the Middle Eastern population. The narratives did not mention any reports of abnormal prenatal ultrasounds (such as for fetal hydrops, which can be detected in other lysosomal storage diseases). Low birth weight (due to prematurity) was reported in three patients' narratives and nine required admissions to the NICU after delivery for respiratory distress.

From the patients' narratives, the mean age of presentation was 2.7 ± 2.5 months. Signs and symptoms at presentation to the documenting physician are detailed in Table 1. Cardiomegaly was documented by either chest x-ray or by typical changes on EKG and cardiomyopathy by echocardiography. More specific details of left ventricular function were not given. The most common physical findings, noted in the narratives, at presentation were hypotonia (94, 75%) and weakness (74, 59%). Respiratory distress was a frequent presenting sign, but only due to infection in 28 (22%). Cardiac failure was also frequently noted as a presenting sign (41, 33%). Feeding problems were relatively infrequent (28, 22%). Hepatomegaly was present in 70 (56%) but splenomegaly was present in only 13 (10%). Macroglossia, common in other storage disorders, was also less frequent as a presenting sign (36, 29%).

Table 1
Signs and symptoms at presentation

Sign/Symptom	*n*	Sign/Symptom	*n*
Hypotonia	94 (75%)	Macroglossia	36 (29%)
Weakness	74 (59%)	FTT	31 (25%)
Respiratory distress	70 (56%)	Hepatomegaly	10 (13%)
Cardiac failure	42 (33%)	Splenomegaly	14 (11%)

Physical exam (Table 2) at presentation showed hypotonia (102, 82%) and weakness (94, 75%) most frequently. Cardiac failure was noted in 62% with a murmur (further details were not specified) in 42%. As the disease progressed (Table 3), hypotonia (66%) and weakness (64%) continued to be prominent physical findings, but the most common finding noted was respiratory distress (72%). Respiratory infection also became more significant (46%). Neurodevelopment was not well documented. Specific milestones mentioned were head lifting (17%), rolling (10%), and sitting (11%). Only 3% were able to weight bear. Formal developmental evaluations were not documented in any patient. Cognitive impairment (2%) and developmental regression (5%) were rare.

According to physician narratives, the diagnosis was confirmed by assaying the activity of α-glucosidase equally in skeletal muscle ($n = 54$, 43%) and skin fibroblasts ($n = 52$, 42%), and less frequently in leukocytes ($n = 29$, 23%). Tissue biopsy (skeletal and cardiac muscle and liver) was done in 54 (43%). Other genetic or metabolic testing was infrequent ($n = 5$, 4% and $n = 15$, 12%, respectively). Mutation analysis was done in eight (6%) patients.

The physicians' narratives noted that 11(9%) patients had surgical procedures, primarily for gastrostomy tube placement; heart transplantation was performed on one patient, who also had a simultaneous bone marrow transplant (without significant improvement). One other patient had a bone marrow transplant, also without improvement. Supportive care with medication was relatively common (Table 4) for control of cardiac (beta blockers and diuretics) and respiratory symptoms (beta agonists and mucolytics), along with noninvasive respiratory therapy, including supplemental oxygen. Mechan-

Table 2
Physical exam at presentation

Signs/Symptoms	*n*	Signs/Symptoms	*n*
Hypotonia	102 (82%)	Cardiomegaly	70 (56%)
Respiratory distress	97 (78%)	Cardiomyopathy	68 (54%)
Weakness	94 (75%)	Heart murmur	52 (42%)
Cardiac failure	77 (62%)	FTT	37 (30%)
Hepatomegaly	76 (61%)	Splenomegaly	14 (11%)

Table 3
Progression of physical findings

Signs/Symptoms	*n*	Signs/Symptoms	*n*
Respiratory distress	90 (72%)	Hepatomegaly	54 (43%)
Hypotonia	83 (66%)	Feeding problems	49 (39%)
Weakness	80 (64%)	FTT	48 (38%)
Cardiac failure	72 (58%)	Macroglossia	25 (20%)
Respiratory infection	58 (46%)	Splenomegaly	11 (9%)

Table 4
Supportive treatments

Treatment	*n*	Treatment	*n*
Cardiac medications	65 (52%)	Respiratory therapy	34 (27%)
Oxygen supplementation	44 (35%)	Respiratory medications	24 (19%)
Mechanical ventilation	38 (30%)	Tracheostomy	16 (12%)

ical ventilation was mentioned in the physicians' narratives in 38 (30%), with some patients requiring multiple episodes of ventilatory support. For 18 (14%) patients, the parents requested active life-support measures. In two of these cases, it was noted that the parents had hope of enzyme replacement treatment in the near future; 16 (12%) had tracheostomies for chronic ventilation.

Psychosocial issues were not well documented in the physicians' narratives. Only seven (6%) patients were referred for hospice care. Counseling of the families about the disease and risk recurrence was only noted in three cases; prenatal diagnosis for future pregnancies was also only noted in three cases. The cause of death was noted in only 29 (23%); many patients died at home, having been cared for by the parents, and the consulting physician was only notified later. The primary cause of death was cardiopulmonary failure. Only six (5%) autopsies were documented.

DISCUSSION

Infantile onset Pompe disease is a rare, devastating, progressive neuromuscular disease with cardiac involvement that typically has onset of symptoms by about 4 months of age and death ensuing from progressive weakness and cardiorespiratory failure by 12 months of age. Few epidemiologic studies have been performed to collect data on the natural history of the disease to date and there have been no reports on the psychosocial impact of the disease. The most comprehensive study is by van den Hout et al.,[2] which reported the natural history data in 153 patients with infantile onset Pompe disease; 20 patients were followed by the authors; the other 133 cases were derived from a review of the literature. Preliminary data from the current natural history study have been presented in abstract form.[3,4]

Typically for this type of study, trained abstractors collect uniform information independently, according to a specific protocol. Physicians who manage patients with this chronic, progressive disease, however, are in a unique position to evaluate the most significant clinical and psychosocial aspects of the disease and the impact on the families, although such information is necessarily subjective and, therefore, difficult to quantitate. As would be expected, however, when compared with the data collected objectively, the physicians noted that the onset of symptoms, physical exam, and progression of the disease is similar. Table 5 shows comparative data for the presenting signs and symptoms collected by the independent abstractors. Surprisingly, however, very little information is given about the psychosocial impact of this disease on the families. One reason for this may be that many of the physicians who participated in this study were specialists at tertiary referral centers who may have seen the patient only to confirm the suspected diagnosis and had little ongoing contact with the families. Another possibility could be the different cultural practices in different countries, where it may be more typical to look after a terminally ill child at home with palliative care, rather than in a large academic medical center. It is also interesting that most of the reporting physicians are geneticists, but there is very little documentation of genetic counseling or discussion of future prenatal diagnosis options. Infantile onset Pompe disease, is a rare disease, consequently, in order to collect significant data, charts from as long ago as 34 years were analyzed. In the intervening years, however, the practice of medicine has evolved to include a greater emphasis on psychosocial support and genetic counseling, which may be another reason that there was little data reported on these issues. Now that enzyme replacement treatment is available for affected infants, clinical practice guidelines will be developed that will hopefully place greater emphasis on these issues.

CONCLUSION

Although the narratives included only what the reporting physicians considered important to include and cannot be compared directly to data collected according to a specific format by the independent abstractors, there is an overall concordance in the description of the most significant clinical aspects of IOPD but there is little information available on the psychosocial impact on families, community support, or genetic counseling.

Table 5
Signs and symptoms at presentation (Objective Data)[a]

Signs/Symptoms	*n*	Signs/Symptoms	*n*
Hypotonia	148 (88%)	FTT	89 (53%)
Respiratory distress	131 (78%)	Cardiac failure	84 (50%)
Weakness	105 (62.5%)		

[a] Data obtained by independent abstractors for natural history study (personal communication, P. Kishnani, 2004).

ACKNOWLEDGMENTS

Support for this study came from Genzyme Corporation, Cambridge, MA. The following physicians have agreed to be acknowledged for their contributed narratives: Joe T.R. Clarke, Hospital for sick Children, Toronto, Canada; Julie Dumont, CCI de Lyon, France; Paul Fernhoff, Emory University, Atlanta, Georgia; Richard Finkel, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Paul Hwu, National Taiwan University, Taipei, Taiwan; Priya Kishnani, Duke University Medical Center, Durham, North Carolina; James Leonard, Institute of Child Health, University of London, UK; Ching-Yuan Lin, Taipei Veteran's General Hospital, Taiwan; Hanna Mandel, Rambam Medical Center, Haifa, Israel; Rick Martin, St Louis Children's Hospital, St Louis, Missouri; Annick Raas-Rothschild, Hadassah University Hospital, Jerusalem, Israel; Daniela Skladal, Universitatsklinik fur Kinder und Jungendheilkund, Innsbruck, Austria; Robert Steiner, Oregon Health and Science University, Oregon; Janet A. Thomas, Children's Hospital Denver, Colorado.

References

1. Hirschhorn R, Reuser AJ. Glycogenosis Type II: acid-alpha glucosidase (acid maltase) deficiency. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. Metabolic and molecular bases of inherited disease, 8th ed. New York: McGraw-Hill, 3389–3420.
2. van den Hout HM, Hop W, van Diggelen OP, Smeitink JA, Smit GP, Poll-The BT et al. The natural course in infantile Pompe's Disease: 20 original cases compared with 133 cases from the literature. *Pediatrics* 2003;112:332–340.
3. Corzo D, Hwu WL, Mandel H, Nicolino M, Yong F, Kishnani P. Natural history of infantile onset Pompe disease: results from a retrospective chart review study. *Mol Genet Metab* 2004;81:170.
4. Marsden DL, Corzo D, Hwu WL et al. The natural history and neurologic manifestations of infantile onset Pompe Disease. *Neurology* 2004;62:S.