ORIGINAL ARTICLE

Mortality in Various Types of Osteogenesis Imperfecta

Richard B. Singer, MD; Simon A. Ogston, PhD; Colin R. Paterson, DM

Mortality Article 826M1

Background.—Osteogenesis imperfecta (OI) is a group of closely related inherited diseases characterized by abnormal bone fragility. The current clinical classification system delineates 6 types, one of which (type II) is so severe that mortality is 100%, either intrauterine or perinatal. The types are differentiated by clinical groups, by severity, and by the presence or absence of other features such as blue sclerae or dentinogenesis imperfecta. There are no known previous studies of mortality in OI.

Results.—From a registry created in association with the Brittle Bone Society, 743 patients with OI in England and Wales were observed in the period 1980–1993. These were classified into 3 groups (type IA, type III, and types IB, IVA, and IVB combined). Average annual mortality rates were determined in each group by sex and attained age. These rates were compared with 1981 rates in the population of England and Wales, matched by sex and age. Results are given in terms of exposures, observed and expected deaths, and 2 indices of excess mortality: mortality ratios and excess death rates per 1000 person-years.

Conclusion.—In type IA, 51.5% of the OI cases overall, there was no significant excess mortality (mortality ratio 108%, based on 15 deaths). In type III, on the other hand, excess mortality was very high in children and still significantly high at ages 15–34 years. In the combined group of types IB, IVA, and IVB, the mortality ratio was 157% in patients aged 45 and up (not significant at the 95% confidence level), but higher ratios at younger ages were significant, even though based on a total of only 5 deaths.

Addresses: Blueberry Lane, C11, Falmouth, ME 04105 (Dr Singer); Department of Epidemiology and Public Health, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, Scotland (Dr Ogston); University of Dundee, Dundee DD1 4HN, Scotland (Dr Paterson).

Correspondent: Richard B. Singer, MD, Consultant to AAIM.

BACKGROUND

Osteogenesis imperfecta (OI) is a large group of heritable disorders characterized by abnormal fragility of bone.[1] It is sometimes called ''brittle bone disease.'' It is the most common cause of fractures in childhood, but patients may also have abnormalities in other tissues, including the teeth, joints, sclerae, blood vessels, and skin. Estimates of the prevalence of the disorder in western Europe and North America vary between 1 in 10,000 and 1 in 20,000.

It is now thought that the great majority of cases of OI result from mutations affecting the formation or structure of type I collagen. While several hundred distinct mutations have been identified, it is usual to classify

Table 1. Sillence Classification of Patients With Osteogenesis Imperfecta

Type	Clinical Features	Inheritance
I*	Mild to moderate severity; little impairment of growth; sclerae are blue or gray through life	Autosomal dominant; new mutations frequent
II	Very severe disease causing stillbirth or early neonatal death	New mutation or parental mosaicism
III	Severe disease with antenatal fractures in many; progressive deformity common; severe impairment of growth; sclerae often blue or gray; dentinogenesis imperfecta common	New mutation, parental mosaicism, or (rarely) autosomal recessive
IV*	Mild to moderate severity; some have growth impairment; sclerae normal in older children and adults but may be pale blue in early childhood	Autosomal dominant; new mutations frequent

* Subdivided into A (no overt dentinogenesis imperfecta) and B (dentinogenesis imperfecta present).

Table 2. Distribution and Other Data of Osteogenesis Imperfecta Patients in This Study

OI Type	Male	Female	Total	Percentage of Total	Exposure (Patient-Years)	Number of Deaths
IA	171	272	383	51.5	3370	15
IB	26	51	77	10.4	719	4
IVA	44	46	90	12.1	977	5
IVB	37	33	70	9.4	714	7
Subtotal	107	130	237	31.9	2410	16
III	53	70	123	16.6	1160	26
Total	331	412	743	100.0	6940	57

cases on clinical grounds as proposed by Sillence.[2] Table 1 summarizes this classification. While both types I and IV are usually described as mild to moderate, type IV patients tend to have more fractures; within type I, patients with type IB tend to have more fractures than those with type IA.[3]

Prior to the publications from Dundee[4,5] there has been no information on mortality in OI. These were based on a registry of cases mainly from the United Kingdom and the Republic of Ireland, ascertained largely through an association with the Brittle Bone Society. The registry was initiated in 1980 and currently consists of over 1450 patients. In this article, we have drawn on the database used in a study of life expectancy[4] to determine for insurance purposes the mortality in the different types of OI.

SUBJECTS STUDIED AND FOLLOW-UP

Patients with OI were drawn from a database prepared for a study of life expectancy in OI.[4] The observation period was January 1, 1980, to January 1, 1993, but patients registered prior to 1980 were given that date for entry into follow-up. Patients were excluded if they were type II, if the type could not be determined, if they were not resident in England or Wales, or if the diagnosis was only made after death. After these exclusions, there were 743 patients in England and Wales remaining for study. Distribution by type and sex is given in Table 2 along with other data (type II is omitted). Over 50% of the patients were in the least severe type IA. The other types shown had a prevalence ranging from 9.4 to 16.6% (type III). After examination of

Table 3. Comparative Mortality in Osteogenesis Imperfecta Type IA—383 Patients in England and Wales, 1980–93

Attained Age or Sex	Exposure (Patient-Years) E	Observed Deaths d	Expected Deaths* d′	Mortality Ratio % 100d/d′	Mean Annual Mortality Rate/1000		
					Observed q	Expected q′	Excess 100(q − q′)
0–24	1728	1	0.78	128	0.5	0.6	−0.1
25–44	1005	1	0.97	103	1.0	1.0	0.0
45 up	638	13	12.16	107	20.0	19.0	1.0
Male	1483	8	5.72	140	5.4	3.9	1.5
Female	1887	7	8.19	85	3.7	4.3	−0.6
Total	3370	15	13.91	108	4.5	4.1	0.4

* Basis of expected deaths is 1981 English Life Tables.

Table 4. Comparative Mortality in Osteogenesis Imperfecta, Types IB, IVA, and IVB Combined—237 Patients in England and Wales, 1980–93

Attained Age or Sex	Exposure (Patient-Years) E	Observed Deaths d	Expected Deaths* d′	Mortality Ratio % 100d/d′	Mean Annual Mortality Rates/1000)		
					Observed q	Expected q′	Excess (q − q′)
0–24	1311	2	0.60	335	1.5	0.5	1.0
25–44	705	3	0.73	410	4.3	1.0	3.3
45 up	394	11	6.99	157	28	18	10
Male	1041	9	3.05	295	8.6	2.9	5.7
Female	1369	7	5.26	133	5.2	3.9	1.3
Total	2410	16	8.31	193	6.6	3.4	3.2

* Basis of expected deaths is 1981 English Life Tables.

the mortality in these rather small groups of patients, we decided to show the higher mortality in type III separately but to combine patients with OI types IB, IVA, and IVB into a single group, with a prevalence of 39.9% and 16 of the total 57 deaths observed in an overall exposure of 6940 patient-years. In type IA, there were 15 deaths, and in type III, there were 26 deaths in a much smaller exposure. Females outnumbered males by a considerable margin. Mean attained age was 24.0 years for the male and 26.8 for the female OI patients.

RESULTS

Excess mortality was minimal and not statistically significant in the type IA patients, with 15 observed and 13.91 expected deaths and an overall mortality ratio (MR) of only 108% and excess death rate (EDR) of 0.4 extra deaths per 1000 per year (Table 3). There was a sex difference, however, with an MR of 140% for the male patients (not significant even at a 10% significance level) and 85% for the female patients. There were only 2 deaths under age 45 so that the overall experience is based predominantly on adults 45 years and older.

As shown in Table 4, for the combined group, types IB, IVA and IVB, excess mortality was significantly high for males (MR 295%) but not for females (MR 133%). Overall, with 16 observed and 8.31 expected deaths, the MR was barely significant at the 5% significance level (just outside 95% confidence limits). Despite only 5 deaths in the 2 younger age groups, the excess mortality was

Table 5. Comparative Mortality in Osteogenesis Imperfecta, Type III—123 Patients in England and Wales, 1980–93

Attained Age or Sex	Exposure (Patient-Years) E	Observed Deaths d	Expected Deaths* d′	Mortality Ratio % 100d/d′	Mean Annual Mortality Rate/1000		
					Observed q	Expected q′	Excess (q − q′)
0–4	208	11	0.411	26,000	53	2.0	51
5–9	214	8	0.048	18,600	37	0.2	37
10–34	648	6	0.294	2100	9.3	0.5	8.8
35 up	89	1	0.344	290	11.6	3.9	7.7
Male	551	7	0.618	1130	12.7	1.1	11.6
Female	609	19	0.419	4500	31	0.7	30
Total	1160	26	1.097	2400	23	0.9	22

* Basis of expected deaths is 1981 English Life Tables.

high enough to be statistically significant, but this was not true for the MR of 157% in patients age 45 and up, based on 11 observed deaths. The overall annual EDR was 5.7 per 1000 for male patients but only 1.3 per 1000 for females.

Almost all of the exposures and deaths were found at ages under 35 years in the type III cases (Table 5). Extremely high and significant excess mortality was present in children under age 15 years. In children 0–4 years, the MR was 26,000% and the annual EDR 51 per 1000; for children age 5–9 years, these indices were 18,600% and 37 per 1000, respectively. The MR of 2100% at ages 10–34 years was also significant, despite its dependence on only 6 deaths. At ages 35 years and up, only a single death was observed. Despite the results cited above for all other types of OI, EDR was higher in females (30 per 1000) than in males (11.6 per 1000). The corresponding difference in MR was exaggerated by the lower mortality in females; MR was 4500% in females and only 1130% in males, all ages combined.

In the single-page article published in the *British Medical Journal*,[4] Paterson et al provided results in terms of life expectancy in 4 graphs, both male and female for type III and the combined group (no graph was shown for type IA because the authors ''. . . could not distinguish mortality in these patients from that in the general population.'' Additional unpublished data of Paterson et al. have been utilized in this report. In the published article,[4] values of life expectancy were shown at ages 0, 1, 5, 10, 15, 25, 35, 45, and 55 years for type III and for the additional age of 65 in the combined group. The population life expectancies were taken from the 1981 English Life Tables. We have not shown the life expectancy results in this report because life expectancy is never used in risk classification for life insurance. The reader who might have a structured settlement annuity case in which the applicant has OI may consult the original article.[4]

COMMENT

With the very limited numbers of deaths in many of the subgroups, this study is an excellent example of ''the value of small classes,'' a topic discussed at an ALIMDA meeting prior to World War I by Dr Edwin C. Dwight,[6] the Medical Director of the New England Mutual Life Insurance Company, who was an active member of the first Medico-Actuarial Study Committee. Statistical significance, assessed by the Poisson distribution, has been shown to exist for some MR values in this article with as few as 6 deaths (type III patients age 15–34 years, Table 5).

Readers who wish to apply these results to construction of ratings for an underwriting manual should be cautioned that MR values

based on population-expected rates must be adjusted upward to allow for the fact that select insurance mortality rates are much lower than population mortality rates. The adjustment process to convert population-expected MRs to numerical ratings has been described in detail.[7] For example, in type IA OI patients, the sex difference in excess mortality should be noted. With an MR of 85% for female patients, it is highly probable that the overall MR based on select mortality would be within a standard limit of 125%. However, the MR for male patients was 140%, with an EDR of 1.5 per 1000. If we assume an average age of 25 years and duration of 5–10 years, the expected select rate from Table 5 of the cited article is 0.96 per 1000. The select MR would then be (EDR + selectq')/selectq' = (1.5 + 1)/1 = 250%, not 140% (this approximate MR would be even higher if the 1990–95 select rate had been used). Male patients with type IA OI therefore do not appear to be eligible for standard life insurance, as female patients would be. Type III patients are generally declinable for life insurance because of the very high level of their excess mortality, but after suitable adjustment, many patients of types IB, IVA, and IVB would probably be eligible for life insurance with an appropriate rating.

REFERENCES

1. Paterson CR. Osteogenesis imperfecta and other heritable disorders of bone. *Baillieres Clin Endocrinol Metab.* 1997;11:193–213.
2. Sillence D. Osteogenesis imperfecta: an expanding panorama of variants. *Clin Orthop.* 1981;159:11–25.
3. Paterson CR, McAllion S, Miller R. Heterogeneity of osteogenesis imperfecta type I. *J Med Genet.* 1983; 20:203–205.
4. Paterson CR, Ogston SA, Henry RM. Life expectancy in osteogenesis imperfecta. *BMJ.* 1996;312:351.
5. McAllion SJ, Paterson CR. Causes of death in osteogenesis imperfecta. *J Clin Path.* 1996;49:627–630.
6. Dwight EC. The value of small classes. *Proc Assoc Life Insur Med Dir Am.* 1913;15:210–218.
7. Singer RB. The conversion of mortality ratios to numerical ratings. In: Singer RB, Kita MW, and Avery JR, eds. *Medical Risks—1991 Compend of Mortality and Morbidity,* Westport, Conn: Praeger Publishers; 1994:66–73.