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ROUTINE FORMAL FETAL MOVEMENT COUNTING AND RISK OF ANTEPARTUM LATE DEATH IN NORMALLY FORMED SINGLETONS

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Summary The routine recommendation to women to count fetal movements daily during late pregnancy for the prevention of antepartum late fetal death in normally formed singletons has been evaluated. 68 000 women were randomly allocated within thirty-three pairs of clusters either to a policy of routine counting or to standard care, which might involve selective use of formal counting or informal noting of movements. Antepartum death rates for normally formed singletons were similar in the two groups, regardless of cause or prior risk status. Despite the counting policy, most of these fetuses were dead by the time the mothers received medical attention. The study does not rule out a beneficial effect, but at best, the policy would have to be used by about 1250 women to prevent 1 unexplained antepartum late fetal death, and an adverse effect is just as likely. In addition, formal routine counting would use considerable extra resources.

Introduction

ABOUT three-fifths of all perinatal deaths of normally formed singletons are late (beyond 28 weeks) antepartum deaths.[1] There is no obvious cause for about 70% of these deaths,[1] most are unpredictable, and the extent to which they can be prevented by current antenatal care is limited. Because these deaths may be preceded by reduction or cessation of fetal movements for a day or more,[2] recognition of such reduction, followed by action to confirm jeopardy and expedite delivery, might prevent such deaths. Thus formal fetal movement counting has been proposed as a routine screen in all pregnancies to identify fetuses likely to be compromised, rather than formal counting in high-risk cases or leaving it to women to note changes in movements informally. The value of fetal movement counting for predicting fetal death appears to be good.[3] In a small controlled trial Neldam[4,5] showed that routine formal counting was associated with a significantly lower rate of antepartum death among normally formed babies weighing more than 1500 g than informal noting. This finding was not predicted before the trial, however, and a non-randomised cohort study of 20 000 women failed to identify any such benefit.[6]

Routine formal fetal movement counting would involve substantial resources for maternity services and for the women. In view of uncertainties about effectiveness, we have done a large, multicentre, international, randomised controlled trial. The study had two main aims: to assess

TABLE I—NUMBERS OF TRIAL PARTICIPANTS

Country	Pairing (within or between hospitals)	Counting			Control			All		
		Clusters	Pregnancies	Singleton births	Clusters	Pregnancies	Singleton births	Clusters	Pregnancies	Singleton births
UK	Within	19	18 344	18 143	19	18 734	18 526	38	37 078	36 669
UK	Between	4	3357	3326	4	5363	5306	8	8720	8632
Belgium	Between	5	5635	5565	5	5933	5824	10	11 568	11 389
Sweden	Between	3	3646	3611	3	4951	4907	6	8597	8518
Ireland	Within	1	455	450	1	451	448	2	906	898
USA	Between	1	556	553	1	1229	1220	2	1785	1773
		33	31 993	31 648	33	36 661	36 231	66	68 654	67 879

whether routine formal counting, backed by appropriate action, results in a clinically important reduction in the rate of antepartum late death in normally formed singletons (without concomitant increase in the rate of intrapartum fetal death, death before discharge from hospital, or specified neonatal morbidity), and to examine wider implications of such a policy for the women and their perinatal services.

Subjects and Methods

Trial Policies

After trial entry at 28–32 weeks' gestation, women allocated to the experimental policy were asked to count fetal movements routinely every day. They were taught, usually by specially employed midwives, to record the time taken to feel ten movements on a modified Cardiff "count-to-ten" chart.[7] This method concentrates on those most at risk: women with vigorous fetuses count for short periods of time whereas those with quiet fetuses monitor for longer. The Cardiff method is simpler than an individualised system and the most widely used in the UK. In our version counting could start as early in the day as was convenient and women were instructed to contact the hospital if movements were reduced. We chose a definition of reduced fetal movements (an alarm) primarily to give sufficiently high specificity. Alarm was defined as no movements on a single day or less than ten movements in 10 h on 2 successive days (except in Belgium where less than ten movements on a single day was deemed sufficient). Women allocated to the control policy were not instructed to monitor movements routinely. They could raise concerns, could be asked about fetal movements at antenatal visits, and obstetricians could give charts to selected women when indicated. For both policies clinicians were asked to respond to reports of reduced movements as they deemed appropriate (eg, cardiotocography and ultrasound).

Design and Entry

Information sheets were given to participating obstetricians to distribute to their patients at booking. 12 obstetricians in the control group chose not to give this information, because they thought it made no sense to tell women that they were not changing their practice. Community midwives and general practitioners were also notified about the trial. The trial received approval from all the ethics committees of the hospitals involved.

The study was a multicentre, randomised controlled trial with "cluster" allocation. The clusters (about 1000 women each) consisted of all women who would be receiving maternity care from an obstetrician, clinic, or hospital during recruitment. The risk of antepartum late fetal death for every cluster was estimated, principally from death rates for the fetuses of women who had received the same type of care in the previous 5 years. The clusters were matched into pairs based on this estimate and randomly allocated to the experimental or control policy within the matched pairs. Random allocation of individual women would have risked "contamination" between the groups, leading to blurring of the separation between the two policies. Also late fetal deaths are rare and large sample sizes are required to control for chance variations in estimates of their frequency; cluster allocation simplified the organisation of the trial, making large samples feasible.

After a pilot study in one hospital during 1985, recruitment began in 1986 and continued for 21 months in most centres. All women within a particular pair of clusters were deemed to have entered the trial at a fixed gestational age between 28 and 32 weeks, the exact gestation depending on the usual time at which women were routinely seen.

Sample Size

The rate of late fetal death in normally formed, antepartum singletons at the time the trial was designed was estimated at about 4 per 1000 total births.[9] With 1:1 random allocation of individual women, a total sample of nearly 60 000 would be needed to have an 80% chance of detecting a reduction by a third to 2·7 per 1000 at the 5% level of significance. Allocation in clusters reduces statistical power because the individuals in a cluster are not independent. Computer simulations (M. J. Shipley, London School of Hygiene and Tropical Medicine) suggested that allocation of 60 000 women in clusters of 1000 would reduce power from 80 to 73%. Variations in the underlying death rate for the clusters, reduction in the number of pairs, or poor matching might decrease the power further.[10] We therefore aimed to recruit at least 60 000 women.

Data Collection and Analysis

Information was collected from delivery books, special care nursery records, and hospital case notes. Classification of deaths was by type of death (antepartum or intrapartum late fetal death, or death before hospital discharge), and by cause.[11] Deaths were also subdivided by the likely impact of the counting policy: (A) "unexplained" deaths were considered most likely to be reduced in frequency; (B) those classified as due to isoimmunisation, maternal disease and infection, and pre-eclampsia were considered likely to be only marginally influenced; and (C) those due to malformation, antepartum haemorrhage, and mechanical problems were judged not at all likely to be influenced. Deaths classified as (A) or (B) were considered "potentially avoidable" by the counting policy. To clarify whether fetal movement counting should be targeted at selected groups, the deaths were also classified by risk markers already present at entry, and at any time during pregnancy. All the deaths were classified initially by obstetricians not connected with the trial who were "blind" to the random allocation and then by one of us. The independent obstetrician was the arbiter in the few cases where there was disagreement.

During 10 weeks in the middle of 1987 (in-depth phase), more detailed data were collected in twenty-six pairs of clusters by postal questionnaires sent to all women who delivered during this period

TABLE II—REDUCED FETAL MOVEMENTS AND USE OF RESOURCES (PER 1000 WOMEN)

Reduced fetal movement	Clusters		Difference in means (95% CI)
	Counting (n = 26)	Control (n = 26)	
Reports			
Total	84 (12)*	65 (9)	19 (0·4 to 38)†
By telephone	15 (4)	6 (2)	9 (3 to 15)†
⩾1 ultrasound scan	10 (2)	6 (2)	4 (−3 to 10)
⩾1 cardiotocogram	74 (10)	54 (10)	19 (2 to 37)†
⩾1 antenatal admission	33 (5)	24 (4)	8 (−3 to 19)
Induction or elective caesarean	16 (4)	12 (4)	4 (−3 to 11)

*Mean (SE); †$p < 0·05$.

TABLE III—RATES OF ANTEPARTUM LATE FETAL DEATH PER 1000 NORMALLY FORMED SINGLETON BIRTHS

Rate	Clusters		Difference in means (95% CI)
	Counting (n=33)	Control (n=33)	
All	2·90 (0·33)	2·67 (0·27)	0·24 (−0·50 to 0·98)
Potentially avoidable	2·17 (0·30)	2·23 (0·25)	−0·06 (−0·76 to 0·64)
Unexplained	1·77 (0·28)	1·85 (0·24)	−0·08 (−0·80 to 0·64)

(except, for compassionate reasons, when the baby had died, was ill, or had been given for adoption or when the mother was ill). Information about antenatal tests and interventions and implementation of the policies was retrieved from case notes and further data were extracted from fetal movement charts.

In most centres data were collected by specially recruited clerks and returned weekly to the coordinating centre at the National Perinatal Epidemiology Unit, Oxford. For eight clusters (in Belgium[12] and the USA) the data were extracted from hospital computerised data collection systems and then added to the trial data base.

Analysis was on an "intention to treat" basis. For every pair of clusters, a summary statistic (such as a mean or proportion) was calculated for the two policies and the differences between them. Then these three figures were averaged over all the pairs. Where relevant, significance was tested with paired t tests and the normal approximation to Fisher's permutation test, with 95% confidence intervals (CI) for differences between clusters.[13]

Results

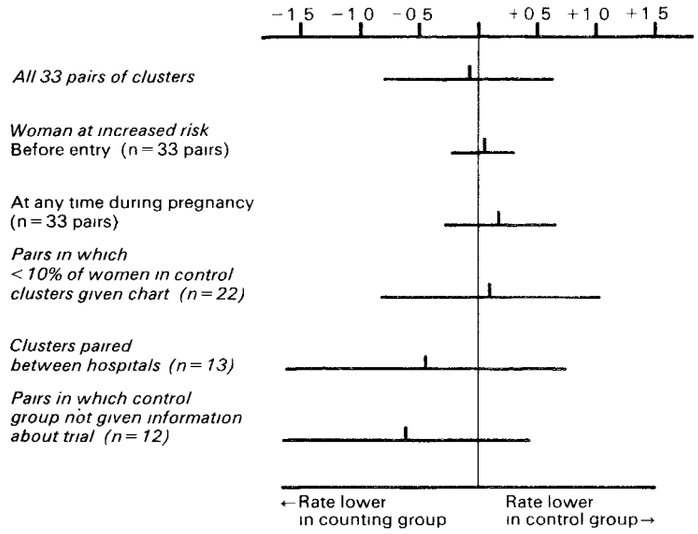
68 654 women (sixty-six paired clusters) participated (table I). The randomised groups were similar in terms of maternal age (means 26·5 [SE 0·2] years), primiparity (44·2 [0·9] versus 44·6 [0·9]), and multiple pregnancies (means 1·1 [0·1]).

Twenty-two UK, all three Swedish, and the one Irish pair of clusters took part in the in-depth phase, which included 12% of women in these centres. The average proportion of women for whom information was available from questionnaires (returned when the baby was a mean 20 days old) was 65%, and from case notes 91%. Fetal movement charts were available for 45% of women in the counting clusters and 0·4% in the control clusters.

There was a clear separation between the two policies. For instance, the questionnaires showed that 89·6% (SE 1·7) of the women in counting clusters were given fetal movement charts compared with 8·9% (1·6) of the controls. 80·6% (2·5) of the women in counting clusters compared with 6·9% (1·3) of the controls completed the chart; corresponding figures for daily completion were 58·9% (3·0) and 4·3% (1·0), respectively. The charts were first used at 30·2 (0·3) and 33·0 weeks (1·1, n=6) in the counting and control clusters, respectively. These figures conceal some between-pair differences, with 4 of the non-counting clusters reporting in the case notes that more than 10% of women were given a fetal movement chart in particular circumstances (eg, on admission).

Based on the returned charts from the counting clusters, women counted for an average of 2·7 h per day (161 h per pregnancy). About 7% of the charts showed at least one alarm (and 1% had five or more alarms). 46% of women whose charts showed at least one alarm had reduced movements recorded in their case notes. Routine counting generated more reports of reduced fetal movements, although not always because of alarms that had been charted. Use of resources was increased as a consequence (table II).

There were few sociopsychological implications of the policies. A slightly higher proportion of women in the counting group felt very or quite anxious in late pregnancy (difference in mean 2·0 per 100 women [95% CI −1·8 to 5·8]). Women in the counting group were also slightly more likely to feel "in control" and confident during this stage of pregnancy. There were no significant differences between the groups in these respects, except in terms of anxiety about filling in fetal movement charts (difference in means 8·6 [6·1 to 11·0]). 33% of women in both groups, however, reported anxiety about reduced movements at some time during late pregnancy.



Differences between counting and control groups in mean (95% CI) rates of unexplained late fetal deaths per 1000 normally formed singletons.

There were 99 antepartum late deaths in normally formed singletons in the thirty-three counting clusters and 100 in the thirty-three control clusters. Table III shows mortality rates for deaths judged potentially avoidable by fetal movement counting and for deaths classified as unexplained. Routine formal fetal movement counting had no advantageous effect on the death rates. Stratified analyses based on risk status and in those strata in which the two policies were most likely to have been distinct did not show

TABLE IV—PREGNANCIES THAT ENDED IN UNEXPLAINED LATE FETAL DEATH: VITAL STATUS WHEN MOTHER FIRST EXAMINED ANTEPARTUM*

Reason for examination	Clusters	
	Counting (n=59 fetuses)	Control (n=58 fetuses)
Dead when first examined		
Reduced or absent fetal movements as per counting policy	7	0
Reduced or absent fetal movements but later than specified	21	16
Other (eg, routine antenatal clinic, in labour, abdominal pain)	20	35
Not known	0	1
	48	52
Alive when first examined		
Reduced or absent fetal movements as per counting policy	6	0
Reduced or absent fetal movements but later than specified	1	0
Other (eg, abdominal pain, inpatient for induction, suspected IUGR)	4	6
	11	6

*Based on deaths on UK, Sweden and Ireland.
IUGR = intra-uterine growth retardation

any differential effect on the risk of unexplained, antepartum late fetal death (figure). The case notes of the 117 unexplained deaths in UK, Irish, and Swedish clusters showed that the counting policy led to only a small reduction in the number of jeopardised fetuses that were dead when they reached formal medical care, despite an earlier response by their mothers to reduced fetal movements (table IV). An estimated 50% of these women completed a chart, with a higher rate when the baby weighed 2500 g or more at birth. In none of the 17 cases where the fetus was still alive on reaching formal medical care was emergency delivery attempted after reduced movements had been recognised. This reflected false reassurance from diagnostic testing, especially cardiotocography, and clinical error.

There was no significant concomitant rise in the rate of death among normally formed singletons after the onset of labour or before hospital discharge (1·71 per 1000 births in the counting group versus 1·31 in the control group). Nor were there significant differences between the groups in the rates of specified neonatal morbidity, such as major malformations (4·04 versus 4·56) and seizures (1·00 versus 1·58). (Calculations are based on the 20 within-hospital pairs of clusters.)

Discussion

This study has confirmed the importance of late fetal deaths among normally formed singletons as a component of perinatal mortality; nearly half of the 446 deaths were in this category. The overall rate, however, (less than 3 per 1000 births) was lower than anticipated. This probably reflects a continuing fall in the risk,[3] for which there was evidence during our study. The fall may also be related to an awareness, especially by care givers, of their involvement in the study (the "Hawthorne" effect[14]). The loss of statistical power that this fall implies was partly compensated for by our recruitment of 8000 more women than our target.

Our study provided no significant evidence that a policy of routinely recommending formal fetal movement counting leads to a lower risk of antepartum late fetal death (regardless of category) than a policy allowing selective use in high-risk cases or informal noting by women. The study does not rule out a beneficial effect (at best [lower 95% CI], about 1250 women with a singleton pregnancy would have to be asked to count to prevent 1 unexplained antepartum death) but the policy is just as likely to have an adverse effect. An alternative to routine counting is restriction of the policy to pregnancies deemed in early pregancy to be at increased risk of late fetal death. However, secondary analyses stratified by risk status failed to demonstrate a beneficial effect in this subgroup.

Could blurring of differences between the two policies explain the lack of any beneficial effect? One possible reason for a loss of contrast between the two policies is poor compliance in the counting clusters. Recording of fetal movements was satisfactory: the rate for charting counts (81%) was in agreement with or higher than the few estimates obtained elsewhere.[3,5,15,16] The rate for reporting alarms (46%) was, however, lower than the 63% found by Valentin et al[15] and compliance, for charting and reporting alarms, was lower among women who had a late fetal death. Although selected women allocated to the control policy could be given charts, when clinically indicated, control obstetricians did not use this option over-enthusiastically: on average 7% of women in these clusters reported using a chart at some time during pregnancy. The use of movement charts by control women did vary between centres although analyses limited to the pairs in which less than 10% of women in the control clusters were given a chart yielded similar results to the analysis of all pairs. Differences between the policies might have been blunted by changes in the attitudes of care givers to fetal movements as a consequence of participation in the trial. This was the potential drawback of within-hospital pairing (the advantage was better matching). Analyses stratified by whether pairing was within or between hospitals slightly suggested this (figure, not significant). Differences between the policies might have been diluted by information given to control women when they booked, which might have made the women more aware of fetal movements. Analyses stratified by whether or not information was given to control women failed to demonstrate any significant difference.

We chose the definition of an alarm used in most centres primarily to limit the number of false positives to an acceptable level. 7% of women who returned a completed chart had at least one such alarm. A definition based on a single day of reduced movements, as used in Belgian centres, is likely to have an unacceptable false-positive rate and was not associated with any protective effect against antepartum late fetal death in our study. The prime reason for failure of routine counting was low sensitivity. Movement counting should increase the number of jeopardised fetuses that are still alive when they reach formal medical care, where they can then be investigated and delivered if fetal compromise is confirmed. The notes of cases of unexplained singleton late fetal death showed that there was only a small improvement in this respect (19% still alive in the counting groups versus 10% in the controls). Nor did the counting policy lead to more planned or attempted emergency deliveries, because of false reassurance from diagnostic testing and clinical error. False reassurance from diagnostic testing is consistent with the four randomised trials of antenatal cardiotocography, all of which showed a higher mortality rate for normally formed babies in the cardiotocography group.[17]

The introduction of routine fetal movement counting had little, if any, psychosocial effect on women, especially in feelings of anxiety. The high rates reported in an observational study[18] therefore reflect more general concern about fetal movements rather than concern prompted specifically by formal counting.

The implementation of routine formal counting has resource implications. We provided extra midwifery support (10–15 min per woman) to help implement the experimental policy; women counted for about 160 h during pregnancy; 2% more women in the counting group had cardiotocography, and 1% more were admitted. Introduction of a counting policy as routine would use considerable extra resources compared with selective use of formal counting and informal noting. Over a year in England and Wales, this would represent about 140 000 midwifery hours, 90 million hours of pregnant women's time, 13 000 extra cardiotocographs, and 5000 more admissions.

Our results do not indicate that maternally perceived reduction in fetal movements is clinically unimportant. Rather, routine daily counting by women, followed by appropriate action when movements are reduced, seems to offer no advantage over informal inquiry about movements during standard antenatal care, and selective use of formal counting in high-risk cases. Better compliance with counting, reporting, and acting on reduced movements might improve performance to make formal counting useful

in high-risk cases, possibly with an individualised scheme and a more lenient definition of an alarm to reduce false-negative results.

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REFERENCES

1 Scottish Health Service Common Services Agency, Information and Statistics Division. Scottish stillbirth and neonatal death report 1987. Edinburgh: Common Services Agency, 1988.
2. Sadovsky E, Yaffe H. Daily fetal movement recording and fetal prognosis. *Obstet Gynecol* 1973; **41:** 845–850.
3. Grant A, Elbourne D. Movement counting for assessment of fetal wellbeing. In: Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. Oxford: Oxford University Press, 1989: 440–54.
4 Neldam S. Fetal movements as an indicator of fetal well-being. *Lancet* 1980; i: 1222–24.
5. Neldam S. Fetal movements as an indicator of fetal well-being. *Dan Med Bull* 1983; **30:** 274–80.
6. Lobb MO, Beazley JM, Haddad NG. A controlled study of daily fetal movement counts in the prevention of stillbirths. *J Obstet Gynaecol* 1985; **6:** 87–91.
7. Pearson JF. Fetal movement recording: a guide to fetal well-being. *Nurs Times* 1979; **75:** 1639–41.
8. Grant A, Hepburn M. Merits of an individualized approach to fetal movement counting compared with fixed-time and fixed-number methods. *Br J Obstet Gynaecol* 1984; **91:** 1087–90.
9. Scottish Health Service Common Services Agency, Information Services Division. Scottish stillbirth and neonatal death report 1985. Edinburgh: Common Services Agency, 1986.
10. Shipley MJ, Smith PG, Dramaix M. Calculation of power for matched pair studies when randomisation is by group. *Int J Epidemol* 1989; **18:** 457–61.
11 Cole S. Hey E, Thomson A. Classifying perinatal death: an obstetric approach. *Br J Obstet Gynaecol* 1986; **93:** 1204–12.
12. Alexander S, Martens G, Bodson L, et al. Transfert direct de données obstetricales sur support magnétique dans le cadre d'un essai multicentrique randomisé du compte subjectif des mouvement foetaux par la future mère. *Rev Fr Gynécol Obstét* 1989; **84:** 179–82.
13. Donner A, Donald A. Analysis of data arising from a stratified design with the cluster as unit of randomisation. *Stat Med* 1987; **6:** 43–52.
14 Roethlisberger FJ, Dickson WJ. Management and the worker Cambridge, Mass: Harvard University Press, 1939.
15 Valentin L, Maršal K, Gullberg B. Subjective recording of fetal movements II. screening of a pregnant population; methodological aspects. *Acta Obstet Gynecol Scand* 1986; **65:** 639–44.
16 Valentin L. Fetal movements in late pregnancy—detection of fetal jeopardy by objective recording and maternal counting. Doctoral dissertation. University of Lund, Sweden, 1986.
17. Grant A, Mohide P Screening and diagnosis in antenatal care. In: Enkin M, Chalmers I, eds. Effectiveness and satisfaction in antenatal care. Clinics in Developmental Medicine No 81/82. London: Spastics International Medical Publications/William Heineman Medical Books, 1982: 22–59.
18. Draper J, Field S, Thomas H, Hare MJ. Women's views on keeping fetal movement charts. *Br J Obstet Gynaecol* 1986; **93:** 334–38.

PREDICTION OF SEVERITY OF GAUCHER'S DISEASE BY IDENTIFICATION OF MUTATIONS AT DNA LEVEL*

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Summary The polymerase chain reaction was used to detect four mutations in the DNA of 47 unrelated patients with type I Gaucher's disease (94 Gaucher's disease alleles). Two of the mutations, 1226 and 1448, and a new mutation (XOVR) representing cross-over between the glucocerebrosidase gene and its closely linked pseudogene, were found. There were five genotypes—namely, 1226/1226, 1226/1448, 1226/XOVR, 1226/?, and ?/? (where "?" indicates that none of the four known mutations was present). Severity of the disease was assessed with a scoring index according to age at diagnosis and extent of organ involvement. Mutation 1226 was associated with a mild clinical phenotype, and mutation 1448 with a more severe phenotype. Mutation 1226 is the most common cause of Gaucher's disease in Jewish patients.

Introduction

Gaucher's disease, a glycolipid storage disorder, is due to a genetically determined deficiency of the enzyme glucocerebrosidase.[1] Of the three types of the disease, type I or "adult" disease predominates; it is characterised by accumulation of glucocerebroside in the spleen, liver, and bone marrow, but the central nervous system is spared.[2] Type I Gaucher's disease is probably the most common inherited disorder among the Ashkenazi Jewish population. The clinical severity of the disease, even among individuals with the same ancestry, varies considerably and there is no correlation between the biochemical abnormalities and clinical course. Therefore, prediction of outcome and genetic counselling are difficult.[3]

Clinical observations in different family groupings[4–6] and immunological detection of cross-reacting material and specific activity of the residual enzyme[7] pointed to genetic heterogeneity in type I disease. Application of molecular biology techniques has provided additional unequivocal evidence for heterogeneity of this disease at the level of the glucocerebrosidase gene.[8–10]

A tightly-linked pseudogene that is highly homologous with the gene for glucocerebrosidase greatly complicates the detection of mutations that cause Gaucher's disease. However, with knowledge of the complete genomic sequence of both the human glucocerebrosidase gene and the glucocerebrosidase pseudogene,[11] we devised polymerase chain reaction (PCR) techniques to detect four mutations that cause the disease.[9,10,12,13] We now report the relation between these mutations and severity of the disease, and describe a new type of mutation.

Patients and Methods

Patients

47 unrelated patients (29 female, 18 male) with type I Gaucher's disease were studied. Diagnosis was confirmed by demonstration of

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