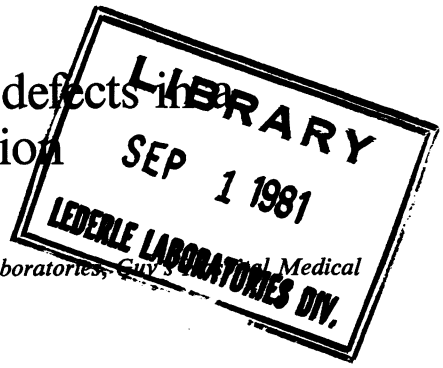
Journal of Medical Genetics, 1981, **18**, 245–248



Recurrence risks for neural tube defects in a genetic counselling clinic population

MARY J SELLER

From the Paediatric Research Unit, The Prince Philip Research Laboratories, Guy's Hospital Medical School, London SE1 9RT.

SUMMARY The recurrence of neural tube defects (NTD) in the sib following the index case of all patients who consulted the South-East Thames Regional Health Authority Genetics Centre in the period 1972 to mid-1979 was calculated. A total of 1037 consecutive patients was studied, of whom 958 (93%) were traced. The overall recurrence was 3·44% (1 in 29). However, if the index case was the first affected child in the family, the recurrence in the next sib was 3·15% (1 in 32), and if it was the second affected child, the recurrence was 11·76% (1 in 9). These figures give an indication of the actual recurrence among the 'selected' population who consult a genetic advice centre, and are somewhat, but not significantly, different from figures for the general NTD population, which have been derived from studies of whole families.

A significant part of the workload of genetic counselling clinics in the United Kingdom consists of advising couples of the risk of occurrence of neural tube defects (NTD) in their offspring, either because they have a previous affected child, or because there is a strong family history. The risks given are empirical and are derived from several major, careful, and comprehensive family studies of whole populations.[1–3] Together, these have shown that there is a cline of increasing incidence of NTD from the south-east to the north-west of the United Kingdom, and that, as the frequency of these abnormalities increases, so does the recurrence in sibs. Hence, although the recurrence of NTD in sibs is generally stated to be around 5% for the UK as a whole, in a high incidence area such as Belfast it is 8·87%[3] and in a lower incidence area, Greater London, it is 4·45%.[2] Genetics clinics consequently tend to modify the risks they give to prospective parents according to their geographical location.

Further, it seems that patients who consult genetics clinics are a particular 'special' subgroup of the general population, tending to be selected, often self-selected, and containing an excess of people of the higher social classes.[4] Nevin[5] has recently shown that in Belfast the recurrence of NTD is related to social class, being lower in the higher social classes. If a genetics clinic population is a special group, then recurrence risks derived from studies on the general NTD population might not be appropriate to such a subgroup.

In order to examine this, the recurrence of NTD among patients consulting a genetics clinic in the south-east of England was examined.

Received for publication 9 September 1980

Materials and methods

The study comprised all women who had had a previous child with NTD (the index case) who consulted the South-East Thames Regional Health Authority (SETRHA) Genetics Centre, which is found within the Paediatric Research Unit at Guy's Hospital, for genetic advice during the period mid-1972 to 30 June 1979, who subsequently became pregnant or who were already pregnant. Since January 1975, information about such patients has been stored in computer records; before that, a card index system was in operation. Care was taken to ensure that only patients with a previous affected child or children were included and that the following were excluded: those with a family history only; those where the patient or her husband was affected; those where the previous affected child was by a different spouse; those where the NTD was known to be part of Meckel syndrome (an autosomal recessive condition) or associated with a major chromosome abnormality; and those patients participating in the vitamin supplementation project for the prevention of NTD.[6]

The outcomes of pregnancies of these women were monitored, and the recurrence of NTD in the first pregnancy following consultation resulting in a live or stillborn infant, or a fetus surviving gestation as far as amniocentesis (together called a 'viable' pregnancy), was calculated. The fetuses had to be included because, with the widespread use nowadays of prenatal diagnosis and termination of affected pregnancies, it is within this group that the recurrences of NTD are located more often than in term births. In most cases, this pregnancy represented the next after the birth of the index child; however, in a few, early in the study period when prenatal diagnosis of NTD was in its infancy, it was not. Since the number of such cases is small, they have been included in the total. Spontaneous abortions before amniocentesis were excluded, and if there was a subsequent successful pregnancy this was then counted in the figures. This was done in an attempt to make the study parallel other studies, which are family studies based on the recurrence in sibs, and because, when patients consult a genetics clinic for advice on recurrence, they are concerned with the recurrence in 'viable' pregnancies.

The patients were drawn from south-east London and its suburbs, Kent, East Surrey, East Sussex, and also from parts of Suffolk and Essex.

NTD are defined as symptomatic spina bifida, spina bifida with hydrocephalus, anencephalus, anencephalus with spina bifida, iniencephalus, and encephalocele. Asymptomatic spina bifida occulta and isolated hydrocephalus were excluded.

Results

The results are shown in table 1. There were 1032 index patients, of whom 958 (93%) were traced. In the first pregnancy following consultation at the SETRHA Genetics Centre, which did not result in a spontaneous abortion before amniocentesis, there were 33 NTD, giving an overall recurrence of 1 in 29 (3·44%). The 925 offspring recorded as not having NTD include some with other congenital anomalies.

Although it is the overall recurrence which is quoted from other family studies, it is known that the risk of recurrence is higher after two previous affected offspring than after only one[7]; consequently, these data were separated into those where the index case was the first affected child in the family and those where it was the second affected child. There were 920 traced cases in the first category, among whom 29 (3·15%) had a recurrence of NTD in the next pregnancy, and 38 traced patients in the second, of whom four (11·76%) had another affected child in the subsequent pregnancy. The recurrence is thus 1 in 32 after one affected child, and 1 in 9 after two affected children.

TABLE 1 *Recurrence of NTD in patients having a previous affected child or children in first pregnancy not resulting in miscarriage following consultation at the SETRHA Genetics Centre, 1972–1979*

Index patients	*No*	*No traced*	*Outcome of first pregnancy (not miscarriage) after consultation*		*Recurrence*
			NTD	*Not NTD*	
Total	1032	958 (93%)	33	925	1 in 29 (3·44%)
First NTD in family	991	920	29	891	1 in 32 (3·15%)
Second NTD in family	41	38	4	34	1 in 9 (11·76%)

Discussion

The recurrence risk given in our genetics clinic in the south-east of England (unless modified by other factors in the patient's history) is 1 in 25 after one previously affected child and 1 in 10 after two affected. The present work shows that the actual recurrence among the population of women consulting this gentics centre and given this information is 1 in 32 after one affected child and 1 in 9 after two. The figures for the recurrence after two affected children may be unreliable because of small numbers, but those for the recurrence after one affected child obtained from 920 pregnancies are considered to be more reliably informative. They suggest that within this selected group of women, there is a trend for a lower recurrence of NTD in the next pregnancy than is commonly thought.

The overall figure of 3·44% recurrence (1 in 29) confirms the suspicion engendered when reviewing the work of this genetics centre over 16 years[8] that our finding of 4% of NTD fetuses in amniocenteses undertaken for 'NTD reasons' was not a true recurrence figure, but was artificially high because of the selective referral to us of some NTD pregnancies which were not true recurrence cases.

There figures differ from those found in other studies,[1–3] including that nearest geographically (though not in time), namely the study in Greater London (1965 to 1968).[2] Recurrence figures for Belfast, Greater London, and this study may be seen in table 2 and are 1 in 11, 1 in 22, and 1 in 29, respectively. The difference between the recurrence in Belfast and this study is statistically significant, $p = <0{\cdot}01$, but that between Greater London and this study is not, $0{\cdot}5 > p > 0{\cdot}3$. One explanation for

TABLE 2 *Comparison of recurrence of NTD in SE England from SETRHA Genetics Centre with that of other published studies.*

	No affected / Total	*Recurrence*
Belfast[3]	63	1 in 11 (8·87%)
General NTD population	710	
Greater London[2]	66	1 in 22 (4·45%)
General NTD population	1484	
SE England	33	1 in 29 (3·44%)
Genetics Centre population	958	

the difference may be the incomparability of the way the figures have been derived, for, unlike the present work, other studies have included in the calculations all known sibs occurring both before and after the index cases. In order to examine this point, the recurrence in the sib following the index case in the Belfast[3] and Greater London[2] data has been extracted and is shown in table 3. The difference between the studies persists and the overall recurrence in the sib following the index case is 1 in 13 in Belfast, 1 in 19 in Greater London, and 1 in 29 in the present study. It is therefore suggested that the findings in the present work may truly represent a trend for recurrence of NTD in the south-east of England, and it is a low recurrence in a low incidence area. An explanation for the difference observed between the findings of the present study and that of Greater London may reside in the fact that Greater London contains a far larger and heterogeneous immigrant population than the south-east of England, among whom, particularly those from Ireland, India, and Pakistan, the incidence, and consequently recurrence, of NTD is high.

The actual difference in the recurrence between these two studies might be, in fact, even greater, as there is another important difference in the composition of the two sets of data. Because of the current widespread use of prenatal diagnosis in families 'at risk' for NTD with the therapeutic abortion of affected fetuses, this study has been largely, of necessity, one of the recurrence of NTD at the time of amniocentesis, that is, around the 16th week of pregnancy. The Greater London study was of livebirths and stillbirths, that is, on data derived from pregnancies which survived to at least the 28th week of pregnancy. It is known that many fetuses with NTD are aborted spontaneously, and Creasy and Alberman[9] have estimated that 7·5% are lost between the 16th and 28th week of pregnancy. Consequently, it can be postulated that a proportion of those fetuses detected as having NTD at the time of amniocentesis in my study are destined to abort spontaneously before 28 weeks, and would not be represented in a study comprising stillbirths and livebirths. Thus, there is probably a slight overrepresentation of NTD 'sibs' in my study compared with the Greater London study.

Some patients included in my study have had more than one 'viable' pregnancy following the index case. However, only their first 'viable' pregnancy has been used for the calculations. To include several pregnancies for some patients and only one for others, who might still have more pregnancies given time, would mean that not all patients would be directly comparable. Such results, however, would tend to make this study more like the other studies referred to, where all sibs are counted, and so are mentioned. These data on incomplete families is 34 NTD in 1072 pregnancies after the index cases, an overall recurrence of 1 in 32 (3·2%). If this is then split into those where the index case is the first affected child, the recurrence is 1 in 34 (2·9%), and when the index case is the second affected child it is 1 in 11 (9·1%). This is continuing the trend of a low recurrence and may be getting towards the actual 'practical' recurrence figures for sibs born after the index case. It will be interesting to study this group of women in several years' time when all families are complete, and to compare the figures for all sub-

TABLE 3 *Comparison of recurrence of NTD in first pregnancy, not ending in miscarriage, following index case in SE England from SETRHA Genetics Centre with that of other published studies*

	Recurrence of NTD in sib following the index case					
	Overall		*When index case is First affected*		*Second affected*	
	No affected / No of sibs	*Recurrence*	*No affected / No of sibs*	*Recurrence*	*No affected / No of sibs*	*Recurrence*
Belfast[3]	12	1 in 13	8	1 in 17	4	1 in 4
General NTD population	153	(7·8%)	133	(6·0%)	17	(23·5%)
Greater London[2]	24	1 in 19	24	1 in 18	0	—
General NTD population	445	(5·4%)	432	(5·6%)	13	
SE England	33	1 in 29	29	1 in 32	4	1 in 9
Genetics Centre population	958	(3·4%)	920	(3·2%)	34	(11·8%)

sequent sibs with those for the first pregnancy after the index case.

It must be noted, however, that the true recurrence of NTD must be higher than this for, as previously mentioned, it is known that a significant number of embryos with NTD are aborted spontaneously. Creasy and Alberman[9] have estimated that over the whole period from conception to the 28th week of pregnancy, 54% of conceptuses with NTD are lost in this way, 46% being aborted before 16 weeks. This is emphasised by one patient who was excluded from the study by definition; the pregnancy following the index case ended in a spontaneous abortion before amniocentesis and the abortus when examined was found to have a large frontoparietal encephalocele. It is felt, however, that patients 'at risk' who consult genetic counselling clinics are concerned to hear not the 'true' recurrence figures, but the recurrence in 'viable' pregnancies, that is, in living fetuses from the time of amniocentesis onwards. Further, they are also most immediately concerned with the recurrence in their next 'viable' pregnancy. Thus, it is suggested that the figures from this survey are valid.

I am indebted to Professor P E Polani FRS for valuable discussions on this work, and to Mrs Angela Fenton and Mrs Lara Thompson for help and discussions concerning the computer data.

References

1. Carter CO, David PA, Laurence KM. A family study of major central nervous system malformations in South Wales. *J Med Genet* 1968;**5**:81–106.
2. Carter CO, Evans K. Spina bifida and anencephalus in Greater London. *J Med Genet* 1973;**10**:209–34.
3. Nevin NC, Johnston WP. A family study of spina bifida and anencephalus in Belfast, Northern Ireland (1964 to 1968). *J Med Genet* 1980;**17**:203–11.
4. Maryon-Davis AR. Who's for amniocentesis? An investigation of factors affecting the uptake of prenatal screening for Down's syndrome and neural tube defect in the South-East Thames Region. Thesis: Royal College of Physicians, London, 1978.
5. Nevin NC. Recurrence risk of neural tube defect. *Lancet* 1980;**i**:1301–2.
6. Smithells RW, Sheppard S, Schorah CJ, *et al.* Possible prevention of neural tube defects by periconceptional vitamin supplementation. *Lancet* 1980;**i**:339–40.
7. Carter CO, Roberts JAF. The risk of recurrence after two children with central nervous system malformations. *Lancet* 1967;**i**:306–8.
8. Polani PE, Alberman E, Alexander BJ, *et al.* Sixteen years' experience of counselling, diagnosis, and prenatal detection in one genetic centre: progress, results, and problems. *J Med Genet* 1979;**16**:166–75.
9. Creasy MR, Alberman ED. Congenital malformations of the central nervous system in spontaneous abortions. *J Med Genet* 1976;**13**:9–16.

Requests for reprints to Dr M J Seller, Paediatric Research Unit, Prince Philip Research Laboratories, Guy's Hospital Medical School, London SE1 9RT.