Neural tube defects: a survey of lesion descriptions made by different European pathologists

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Abstract
Recent epidemiological interest has focused on separation of neural tube defects (NTD) into subgroups which may differ pathogenetically and aetiologically, for example, 'upper' and 'lower' spina bifida. In order to validate the use of pathologists' lesion descriptions by epidemiologists and others, a postal survey of 18 European perinatal pathologists, identified by EUROCAT registries, was conducted. Pathologists were asked, anonymously, to describe and identify the lesions in 15 photographs of midtrimester termination fetuses. There was a 50% response rate. Eventaking into consideration the limitations of dealing with photographs rather than the fetuses themselves, there was often marked variation in the descriptions. Standardisation of terminology and international consensus about the type of detail recorded for NTD are urgently needed. (J Med Genet 1993;30:942-6)

Traditionally, neural tube defects (NTD) are broadly divided into 'anencephaly' and 'spina bifida'. Indeed, statistics on birth prevalence of NTD are usually split into these two categories, for example, those produced annually by OPCS for England and Wales1 and by the EUROCAT network.2 However, a number of detailed studies of NTD over recent years have emphasised the heterogeneity of NTD,3-4 and have shown that within the multifactorial type, aetiologically, even more homogeneous groups can be formed by subclassifying NTD according to particular clinical, morphological, or other characteristics. All this has implications for genetic counselling as well as for pathogenesis, epidemiology, and, eventually, prevention.

Various interesting points have emerged, for example, that 'upper' and 'lower' NTD may be different aetiologically4-6 although this has been challenged7,8 that the recurrence risk for sibs of probands with 'high' spina bifida in British Columbia is markedly greater than for those with 'low' spina bifida,9 and that macrocephaly (or complete anencephaly) and holocrania (or complete anencephaly) have a very different sex distribution.8 EUROCAT, a concerted action of the European Community (EC) for the epidemiological surveillance of congenital anomalies, conducted a study involving 13 European registries, the results of which suggested10 that the well known differences in prevalence of NTD between the British Isles and continental European countries differ according to the type of defect. 'Upper' spina bifida, craniorachischisis, and anencephaly were found to be particularly frequent in the British Isles relative to the continental countries. Studies such as this, based on the descriptions of many different observers, have the advantage of large numbers and wide geographical spread compared with single centre studies,11 but the disadvantage that the contributors may use different descriptive systems, which, in addition, often lack precision and detail, so complicating interpretation. Also, terms such as 'upper' and 'lower' spina bifida are not in regular usage. Toriello and Higgins4 defined them as defects at or above T11 and at or below T12, respectively, for their study, most specific and exact. Other people may use a looser definition. For work in this field to be meaningful and to progress, it is crucial that the definition of all the different subgroups of NTD is universal, and their recognition by pathologists and other workers in the field accurate and concordant.

Interest in the heterogeneity of NTD shows no sign of diminishing11,12 and so we sought to investigate further whether there is, in fact, a real problem in the standardisation of terminology and description of neural tube defects. We conducted a small survey of European perinatal pathologists.

Method
The method used was a postal questionnaire with photographs of midtrimester fetuses with distinct NTD. The names of the pathologists were supplied by the EUROCAT registries, and comprised those who have carried out perinatal necropsies in the registry areas.

A pilot study using good photocopies of photographs (as an economy measure) was first undertaken with two pathologists to test the feasibility of our approach, and this led to minor modifications in protocol and in a decision to substitute the photographs for the photocopies. The definitive questionnaire with the photographs was sent with a covering letter to 18 pathologists, who had, in most cases, already had the study explained to them by their local EUROCAT Registry. They were asked to complete the questionnaire in whatever European language they chose, and were assured that their answers would be analysed anonymously.

There were 15 photographs of fetuses with an NTD derived from midtrimester terminations of pregnancy after prenatal diagnosis (six
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are shown in figs 1 to 6). The fetuses themselves had been examined in detail by one of us (MJS). These were specially chosen as being thought to represent specific types or levels of lesions of the neural tube. We sought to determine how particular lesions were named or described by pathologists from the different countries, whether complete and incomplete anencephaly were routinely differentiated, how a combination of anencephaly and a localised spina bifida cystica were described, and how accurately spinal lesions were designated visually as cervical, thoracic, lumbar, or sacral. In the questionnaire the first question asked for a description of each lesion. The second question enquired whether the responder in

Figure 1  Complete anencephaly and cervical and upper thoracic spina bifida cystica.

Figure 2  Sacral spina bifida cystica.

Figure 3  Thoracolumbosacral spina bifida cystica.

Figure 4  Thoracolumbosacral spina bifida cystica.
normal practice estimates the level of a spina bifida cystica lesion visually or by x ray. The third question concerned the definition of a ‘closed’ NTD lesion. This was included because it has been claimed that skin covered, closed lesions are pathogenetically different from open lesions, being more likely to be the result of postneurulation disorders. A fourth question further asked how ‘open’ or ‘closed’ iniencephaly would be differentiated.

**Results**

Replies were received from nine pathologists (50%). Despite this relatively poor response rate, significant findings emerged which we consider relevant to report. The responders came from the United Kingdom, Ireland, Belgium, Denmark, and France (one from each), and four from Holland. One subject was a general pathologist, the remainder neonatal pathologists. Two replies were in Dutch, the others in English. One of the photographs was discarded as, with hindsight, it seemed not sufficiently clear for the replies to be informative. Two photographs were not received by the pilot respondents and one other.

Five respondents stated that they would routinely x ray the fetus to determine the level of a spinal lesion, three would only x ray if specially requested, and one did not answer this question.

Three types of NTD, iniencephaly (a lateral view showing the characteristic configuration), total craniorachischisis (the entire neural tube open), and occipital encephalocele, were identified and described similarly by all respondents.

There were three different anencephalic fetuses, and these were always identified as such, but further description indicating whether the defect was complete (holoacrania) or incomplete (meroacrania) varied. One respondent used the term ‘craniacephalus’ as a synonym for incomplete anencephaly and reserved the term ‘anencephaly’ for complete anencephaly. Two respondents used the terms ‘complete’ and ‘incomplete’, while two further respondents gave descriptions which could be easily interpreted as such a designation: for instance, meroacrania was described as ‘minima anencephalus with absent large brain, but present cerebellum’; and holoacrania was described as ‘total anencephaly (without occipital bone) and probable cervical partial rachischisis’. In holoacrania there is a very short neck, lordosis, and abnormalities of the cervical vertebrae including spina bifida, usually skin covered, and in the case shown, the spina bifida was not overt. Two respondents did not distinguish complete and incomplete anencephaly but one of these identified a cervical spina bifida in the complete case. Another respondent also did not distinguish complete from incomplete anencephaly, but in both cases of incomplete anencephaly the description included the suggestion that the defect was artefactual and had a mechanical origin.

There were two cases of anencephaly and a localised spina bifida cystica. One was complete anencephaly with an open cervical and upper thoracic spina bifida (C1–T2) (fig 1). All identified the anencephaly, three calling it complete, but only six stated that there was also cervical spina bifida. This description is identical to some given for holoacrania. One person used the term ‘craniorachischisis’.

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**Figure 5** Thoracolumbosacral spina bifida cystica.

**Figure 6** Amniotic band disruption: anencephaly, exophthalmos, and facial clefts.
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Only one person mentioned that there was also cervical and 'dorsal' spina bifida. The second fetus had complete anencephaly and a separate lower thoracolumbosacral spina bifida cystica (T11–S5), although the lower part of the sacral lesion was covered by skin. The two separate lesions were noted, but six respondents said the spinal lesion was simply lumbar, and two said it was thoracolumbar.

Of the four cases of isolated spina bifida cystica, the first (fig 2) was solely sacral (S3–5) and two identified it as such. Two said it was lumbar, one low lumbar, and two lumbosacral. Two identified it as a meningocele without specifying location, but one of these further stated that it would be diagnosed as a spina bifida occulta with sinus tract if it were found to be covered by skin rather than membrane.

Two other cases involved identical spinal lesions from T10 to S5 but, in the first (fig 3), the lower lumbar and sacral part was covered proximally by thin membrane and then distally by full thickness skin, although the splayed bony pedicles could be seen beneath; in the second (fig 4), the whole lesion was open and there was kyphosis of the lumbar spine. These were included because, according to one subdivision, they would be 'upper' spina bifidaes (at or above T11). The former case was identified as lumbar by three respondents, and thoracolumbar or dorsolumbar by another three (the remaining three did not receive this photograph). The latter case was stated to be lumbar (2), dorsolumbar (2), thoracolumbar (2), lumbosacral (1), lumbosacral + ? lower thoracic (1), thoracolumbosacral (1).

The final spina bifida cystica case was another thoracolumbosacral lesion but involving the upper thorax (fig 5). This was described either as 'thoracic' or 'dorsal' (3) or thoracolumbar (3) (three respondents did not receive the photograph).

The case of Meckel syndrome (an anterior view of the body and lateral view of the head showing open encephalocoele and postaxial polydactyly on all extremities, cleft lip, bulging abdomen, and small omphalocoele) was correctly identified by all but one respondent, who suggested that it was a chromosomal abnormality, perhaps not too unreasonable when unable to handle the fetus. A further respondent mentioned that a differential diagnosis between Meckel syndrome and a trisomy 13 would be necessary. None of the pathologists considered it necessary to state in a report the mode of inheritance of Meckel syndrome, except one, who stated that it was autosomal dominant rather than autosomal recessive.

A case of amniotic band disruption which could be considered a 'classic' presentation (fig 6), with anencephaly and exphalomes and facial clefts with attached amnio, was identified as such by four respondents. One further respondent said that the placenta would be needed to exclude possible amniotic bands. One respondent said that the malformations indicated a syndrome, or were caused by a teratogen, but did not mention amniotic bands. The other three described this case as "anencephalus with possible proboscis or nasal encephalocele", "anencephalus, encephalocele, arhinencephaly and protruding tongue", and "hydranencephalus with proboscis".

The terms 'open' and 'closed' as related to spina bifida were not universally used, but five respondents would nevertheless interpret 'closed' to mean skin covered. As applied to iniencephaly, most respondents believed 'open' to indicate the presence of an open lesion such as an anencephaly or rachischisis. Other comments were that iniencephaly is always closed by definition, or that it depended on the level of the lesion in the cervical spine.

Discussion

It was not the purpose of our study to classify answers into 'right' and 'wrong', but only to draw attention to the sometimes marked variation between the descriptions of specific lesions given. Although the response rate by pathologists was only 50%, and some caution should be exercised as the survey was based on photographs, which is quite different from being able to examine a specimen, and some pathologists would routinely use x-ray, the results suggest that if NTD are to be subclassified, then standardisation of terms and more precision as to boundaries of lesions are sorely needed.

If the vertebral level of spina bifida cystica is to be determined visually, then this may be sufficient for indicating the upper extent of the lesion, since detailed examination shows that the upper extent of a bony lesion is often similar to the skin lesion, but distally the bony lesion usually extends much further inferiorly than the skin lesion.6 From our study, lumbar spina bifida would seem often to be a general term for a lesion in the mid to lower back, much as 'dorsal spina bifida' is implied when the lesion involves the mid or upper thorax. There was no lesion involving only the lumbar vertebrae in the fetuses in the study, yet the term was used for both a sacral lesion on the one hand, and thoracolumbosacral lesions on the other. The ability of studies based on the descriptions of multiple observers to classify defects into 'upper' and 'lower' spina bifida must therefore be severely limited. Finer subdivisions of NTD still may also be of interest; for example, the six cases of isolated open sacral spina bifida of one of us (MJS) are all male, and confirmation of this trend is possible only if such lesions were reliably identified by other observers.

Some pathologists routinely differentiate between the two different forms of anencephaly, while others do not. A markedly different sex distribution has been found for the two forms.8 With greater numbers, the sex ratios currently stand at 1:17 for meroacrania and 0:55 for holocrania (34 and 26 cases respectively). The fact that the former, which involves the more rostral end of the anterior neuropore, is so much more common in males than females, while the latter, which involves the caudal end of the anterior neuropore, occurs much more often in females, as does total
craniorachischisis and anencephaly and cervical and upper thoracic spina bifida, could well have implications regarding aetiology, and, as with the male preponderance in sacral spina bifida, demands further study involving greater numbers. This will necessitate universal inclusion of this extra detail in necropsy reports and case descriptions, and in coding systems used by congenital malformations registries.

The abundance of synonyms in the terminology relating to neural tube defects has been recognised. Nevertheless, further attention is needed to define the use of terms such as cranioschisis and craniorachischisis. For the latter, we suggest it should only be used for total forms, unless used with further specification (for example, cervical craniorachischisis).

‘Anencephaly’ produced by amniotic band disruption (ABD) was not universally recognised. This has been pointed out by a number of authors. The photograph provided in this study was thought to be ‘classic’. The correct identification is crucial on two counts: firstly for genetic counselling purposes, since in contradistinction to the common multifactorial form of anencephaly, ABD is sporadic and so has a negligible recurrence risk. Secondly, their inclusion as simply ‘anencephaly’ leads to erroneous deductions from studies of characteristics of specific subgroups of multifactorial NTD.

Some authors have claimed that whether a defect is open or closed has pathogenic, and, by implication, aetiological significance. According to Lemire, for example, defects closed by skin indicate that the pathogenetic process was a reopening of a normally formed neural tube rather than faulty neural tube closure. Epidemiological studies cannot easily address this question. Firstly, the meaning of the division between open and closed in terms of skin or membrane covering needs to be clearly defined. British pathologists in particular are probably accustomed to this definition in relation to alphafetoprotein (AFP) screening, where a closed defect is one where AFP cannot leak into the amniotic fluid. Secondly, an open defect can be caused by rupture of the skin during the birth process, and re-epithelialisation before or after birth of an open defect may occur. Further research of clinical series is needed to see whether subgroups can be identified where the open/closed status is of aetiological importance.

Anencephaly was well recognised by respondents. However, there seems to be some difference of opinion over what constitutes an open defect. It is common usage to describe an anencephaly associated with an open neural tube defect such as anencephaly as open. However, in other definitions, an open anencephaly is one where the cranial contents do not remain within the cranial cavity but protrude into an encephalocele (which may be closed by skin). Anencephaly is extremely rare, and in order to collect a series from multiple centres, the descriptive solution would seem to be to describe separately all associated NTDs and, where appropriate, the open/closed status of the associated NTDs.

Our sample of respondents could be said to be highly selected, and we would not claim that the proportion of differing answers would necessarily reflect the community of pathologists as a whole. Further, we did not investigate the conformity of description among paediatricians. We accept that working from photographs is not as satisfactory as an examination of the fetus or baby. However, we do not consider that this can explain entirely the variation in descriptions found in this survey.

We believe that for the future of this interesting and important group of malformations, international consensus about the amount and type of detail about NTD lesions, and the associated terminology, should be reached by pathologists, geneticists, epidemiologists, and other interested parties.

We sincerely thank the nine pathologists who took part in this survey, and the EUROCAT registries who acted as intermediaries.