"Ante-natal diagnosis of central nervous system malformations"

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Introduction

RECENT YEARS have seen the rapid advances in the field of ante-natal diagnosis. Aristotle, in his "History of Animals" refers to the possibility of being able to predict the sex of the unborn child by such criteria as the side on which fetal movements are felt, or even the general condition of the mother. In fact, only in comparitively recent times have precise techniques been developed for the study of the human foetus in utero.

Nowadays, besides being able to ascertain the sex of the foetus antenatally, it is possible to diagnose ante-natally a number of chromosomal and metabolic disorders, as well as malformations of the central nervous system. This review is concerned only with the ante-natal diagnosis of central nervous system malformations.

The central nervous system malformations that would be discussed here are anenecephaly and spina bifida. Anencephaly, with or without spina bifida, is a relatively common congential anomaly in the British Isles, although less common in Malaysia. Once one affected child has been produced there is an increased risk for subsequent children. According to Fraser Roberts, the risk of the next child being affected after one affected child has been produced is 1 in 20; and 1 in 10 or so for a third child, when there are two affected children.

There are a number of methods developed in the diagnosis of malformations of the central nervous system of the foetus in utero.

1) Alfa-fetoprotein

Alpha-feteprotein, first detected in the human foetus in 1957, is the first fetoprotein to appear during foetal development and is the dominant serum protein of early foetal life. It is produced by the foetal liver and yolk sac. It has a molecular weight of about 65,000 and probably consists of a single peptide chain.

In 1972 Brock & Sutcliffe presented clear evidence from a retrospective study that the alpha-fetoprotein (A.F.P.) levels in the amniotic fluids of anencephalic foetuses between 26th and 36th weeks of gestation were much higher than those from unaffected foetuses. Later, again retrospectively, Brock & Scrimgeour (1972) found a high A.F.P. level in the amniotic fluid of an anencephalic of 18 weeks' gestation, suggesting that the levels are high also at earlier stages of such pregnancies.

Thus, the level of A.F.P. in the amniotic fluid obtained by amniocentesis may be a valuable guide to the early ante-natal diagnosis of anencephaly and spina bifida, and thereby enable termination of the pregnancy to be carried out. There is a report by Sellers et al (1973) where anencephaly was diagnosed by a raised level of A.F.P. in the amniotic fluid in a 20 weeks' pregnancy and this was confirmed by ultra-sound examination, where no foetal head could be detected. This pregnancy was subsequently terminated.

Women who are in the "at risk" category (i.e. had one or more affected children) should be "screened". Trans-abdominal amniocentesis could be offered to these patients at about 17 – 18 weeks

of gestation. Technically, if the pregnancy is too early, there could be much difficulty in locating the amniotic sac transabdominally. The mean A.F.P. level for nineteen control amniotic fluids at 17 – 18 weeks' gestation was 15 ug per ml. (range 7 – 22 ug ml). Brock & Scrimgeour found that the level of A.F.P. of an 18 weeks' pregnancy with anencephalic foetus was nine times the upper limit of normal. Lorber et al also found that, in a pregnancy with a foetus with anencephaly and spina bifida, the concentration of A.F.P. in amniotic fluid at 20 weeks' gestation was six times the upper limit of normal. But the closed variety of spina bifida has been reported to give normal levels of A.F.P. These cases account for about 15 per cent of all cases (Laurence, 1974).

High levels of A.F.P. in the amniotic fluid have also been reported in fetal death (Milunsky and Alpert, 1974) and in cases of Turner's syndrome (Seller et al., 1974). On reports so far, false-positive results are relatively rare.

From the above, it would seem that anencephaly or spina bifida can be diagnosed in the foetus in utero by studying the A.F.P. level amniotic fluid at a stage early enough in pregnancy to permit termination.

But for diagnosis of spina bifida in the first half of pregnancy, amniocentesis must be performed. This is unsuitable for "screening" purposes for the general population except for the "high risk" patients. Further, amniocentesis is an "invasive" technique, the effects of which has not been fully evaluated.

It has been shown that the maternal serum level of A.F.P. is elevated in early pregnancy in some cases of spina bifida and anencephaly (Wald, M.J., Brock, D.J.H., and Bonnar, J., 1974; Brock et al, 1974). In a series conducted in Edinburgh and Oxford, it was found that one-third of the mothers with fetuses affected by both types of spina bifida cystica (open and closed) have raised serum A.F.P. levels between 14 and 21 weeks gestation. Multiple pregnancy could give rise to a higher maternal serum A.F.P. level and it has reported that the average maternal serum A.F.P. levels were double these found in singleton pregnancies (Wald et al, 1975). It is therefore vitally important to exclude multiple pregnancy by ultrasonagraphy in cases with elevated maternal serum A.F.P. levels before an amniocentesis is performed to confirm the diagnosis of spina bifida or anencephaly.

2) **Fetoscopy**

Westin (1954) described a technique of hysterophotography performed between 16 and 20 weeks' gestation. The instrument he used had an outside diameter of 10 mm. and was introduced through the cervical canal. He observed foetal limb movements and swallowing when local anaesthesia was used, but neither occurred if a general anaestetic was used. All three of his patients subsequently underwent termination of pregnancy. In another report (Westin, 1957), the foetus was photographed and oxygen tensions in the umbilical vessels assessed, but the pregnancy was immediately terminated.

Scrimgeour, in Edinburgh has pioneered a technique of fetoscopy, of directly inspecting the foetus through a telescope, looking for evidence of central nervous system malformations such as spina bifida and anencephaly. He uses a fibre optic telescope with an outside diameter of 2.2 mm. The telescope was introduced trans-abdominally by a similar size trocar and cannula. To avoid any possible hazard to the developing foetus, a filter has been incorporated in the light source to reduce the ultraviolet and infra-red portion of the light.

Before fetoscopy could be performed, placental localisation is essential. In Edinburgh, ultrasonagraphy was used to localise the placenta before the procedure is carried out. Ultrasonagraphy will also confirm the size of the foetus in relation to its estimated gestation, by measuring the biparietal diameter. Also it could exclude multiple pregnancy where if it is present, would contra-indicate the performance of the procedure. The procedure is carried out under general anaesthesia so that if the foetus is found to be affected, termination by hysterotomy can be performed immediately. The bladder is emptied prior to induction of anaesthesia and strict aseptic precautions are observed throughout the procedure.

Scrimgeour found that the most suitable time for performance of the procedure is between 16 – 20 weeks' gestation. In pregnancies less than 15 weeks, entry into the amniotic sac with the trocar proved difficult. In gestations of more than 20 weeks, the foetus has grown to a size which makes movement in the amniotic sac difficult. The amniotic fluid conducts light easily unless contaminated with bilirubin, meconium or blood.

The complications of fetoscopy are haemorrhage, especially if the trocar goes through an anterior placenta; infection, abortion, premature labour and injury to the foetus. Also the bladder might be injured if it is not emptied before the procedure.

Fetoscopy is still a research tool at present, and is only at the initial stage of development. But it is an invaluable tool as the external appearance of the foetus could be inspected directly. It might, with

greater experience and expertise in its use, become a useful method of early ante-natal diagnosis of congenital abnormalities, such as spina bifida and anencephaly.

3) Ultrasonography

Ultrasonography has been used in the assessment of foetal maturity by serial measurements of the biparietal diameter of the foetal head. Using the ability of ultrasonography to identify the foetal head, it has been tried in the pre-natal diagnosis of anencephaly. Donald (1969) used the ultrasound examination to diagnose anencephaly pre-natally, but it was done only quite late in pregnancy. There has been a report by Campbell et al (1972) of diagnosing an anencephalic foetus at 17 weeks' gestation. In the case report by Campbell, the anencephalic pregnancy was successfully diagnosed by ultrasound 17 weeks after Clomiphene induction of ovulation. The pregnancy was subsequently terminated; the ultrasound was repeated twice at weekly intervals to exclude any possibility of human error before termination was carried out. Termination of the pregnancy could be carried out by intra-amniotic urea or prostaglandins.

Campbell et al recommends that every patient who has delivered an anencephalic foetus or a baby with spina bifida, should be screened with ultrasound early in the second trimester of any subsequent pregnancy. If the diagnosis could be made early enough in the pregnancy, termination of the pregnancy could be carried out.

The advantage of this method is that it is simple and harmless, and causes no discomfort to the patient. Further, it is non-invasive. However, it requires specialised units and elaborate ultrasound facilities are not widely available. It also requires considerable experience in the correct interpretation of the ultrasonagrams. Cases of spina bifida are less likely to be diagnosed by ultrasonography.

4) Other Methods

There are other methods of pre-natal diagnosis of central nervous system malformations. Emery et al (1973), in their study of thirty-three rhesus positive mothers with foetuses affected by central nervous system malformations, found a significant increase in the amount of various animo acids in the amniotic fluid obtained at various stages of gestation. These affected foetuses are anencephalic or have spina bifida or both.

The increase in the amount of amino acids in the amniotic fluid was particularly pronounced in the case of certain neutral amino acids (methionine, isoleucine, leucine, tyrosine and phenylalanine). According to the authors, if the increase of these amino acids in amniotic fluid should prove to be unrelated to foetal distress, then it might be a useful adjunct in the ante-natal diagnosis of central nervous system malformations.

Cassady and Cailliteau (1967) found an increase in the optical density of amniotic fluid at 450 mu. in six out of seven cases of anencephaly. Anencephaly has been shown to be associated in late pregnancy with reduced amniotic fluid levels of 17-ketosteroids, pregnanetriol (Jeffcoate et al 1965), oestriol (Michie, 1966) and certain other cortiosteriods (Lambert and Pennington 1965) but it is not known if these biochemical changes are present in early pregnancy. They are presumably a reflection of adrenal atrophy, which is an associated feature of anencephaly.

Finally, it was observed, at least in the last trimester of pregnancy, a significant reduction in amniotic fluid levels of 5-hydroxy-indoleacetic acid (5HIAA) in central nervous system malformations (Emery et al 1972). The reduced levels of 5HIAA in amniotic fluid may reflect reduced foetal synthesis as a consequence of the reduction in functioning neural tissue in the more severe central nervous system malformations.

Conclusion

Above is a brief summary of the recent advances made so far in the ante-natal diagnosis of central nervous system malformations. It holds exciting prospects for the future. Probably in the not too distant future, many congenital abnormalities of the baby could be diagnosed even before the baby is born.

Acknowledgements

My grateful thanks to Dr. John B. Scrimgeour, Consultant Obstetrician and Gynaecologist, Western General Hospital, Edinburgh for stimulating my interest in the subject. My appreciation also to Miss Patricia Lim for typing the manuscripts.

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