Spina bifida – neural tube defects

Spina bifida – neural tube defects

Basic research, interdisciplinary diagnostics and treatment, results and prognosis

Edited by
D. Voth and P. Glees

In collaboration with
J. Lorber

Walter de Gruyter
Berlin · New York 1986

Prof. Dr. med. Dieter Voth
Klinikum der Johannes-Gutenberg-Universität
Neurochirurgische Klinik und Poliklinik
Langenbeckstr. 1 · D-6500 Mainz

Prof. Dr. med. Paul Glees
University of Cambridge
Department of Anatomy
Downing Street
Cambridge CB2 3DY · Great Britain

This book contains 105 illustrations and 66 tables

CIP-Kurztitelaufnahme der Deutschen Bibliothek

Spina bifida neural tube defects : basic research, interdisciplinary diagnostics and treatment, results and prognosis / ed. by D. Voth and P. Glees. In collab. with J. Lorber. – Berlin ; New York : de Gruyter, 1986.
ISBN 3-11-010768-6
NE: Voth, Dieter [Hrsg.]

Library of Congress Cataloging in Publication Data

Main entry under title:
Spina bifida – – neural tube defects.
Based on the 5th workshop held in Mainz, Sept. 1984. Includes bibliographies and indexes.
1. Spina bifida – – Congresses. 2. Dysraphia – – Congresses.
I. Voth, D. (Dieter), 1935 – . II. Glees, Paul. III. Lorber, John.
[DNLM: 1. Spina Bifida – – congresses.
WE 730 S7573 1984]
RJ496. S74S69 1986 617'.482 85-29183
ISBN 0-89925-149-8 (U.S.)

Dedicated in cordiality to
Professor Dr. Heinrich Bredt,
my academic teacher in pathology,
on the occasion of his 80th birthday.

Mainz, January 1986 *D. V.*

Preface

Malformations resulting from a defective or delayed closure of the embryonic neural tube contribute a significant portion of malformations to human pathology. Although morbidity of the most severe type is decreasing, the presence of dysraphia is a serious medical challenge for modern treatment of the accompanying symptoms, such as for internal hydrocephalus which can preserve life into maturity.

The interdisciplinary multitude of problems caused by dysraphia is bound to involve a number of clinical disciplines such as genetics, pathology, gynecology, neuro- and pediatric surgery, pediatry, orthopedics and urology.

The main purpose of our 5th autumn workshop in Mainz (Sept. 1984) was the combination of these disciplines. Special attention was paid to fundamental aspects and to experimental pathology, the present tools used in antenatal diagnostics and to get an up to date insight of the therapeutic standard.

We express the hope that these published reports of well known specialists in this field will provide a basis for a modern approach both for the benefit of the patient and for the clinician in his decision for the best possible available therapy.

February 1986

D. Voth, Mainz
P. Glees, Cambridge
J. Lorber, Sheffield

Contents

I Pathology and morbidity of neural tube defects

Spina bifida – a vanishing nightmare?

J. Lorber

Introduction

The object of this communication is to draw attention to the declining incidence of spina bifida in many parts of the world, especially in Great Britain, and to outline the role that antenatal diagnosis followed by termination of pregnancies has played in this phenomenon. It is now possible that spina bifida is a disappearing disorder.

In the past, increases in spina bifida births occurred during war, famine or economic disasters. Correspondingly, there was a tendency to steady decline when the circumstances have improved.

Unfortunately, reliable official national statistics over a prolonged period, based on population surveys are still rare. Such statistics are still not available even for many of the medically most advanced countries, including the United States of America. However, from 1980 onwards monitoring was started by the International Clearinghouse for Birth Defects in which more and more countries or groups of hospitals participate. From this some useful short-term information regarding trends is already available. In Europe a beginning has been made by the EEC Concerted Action Project ("Eurocat") which started publishing figures from 1979. These are local, rather than national statistics and so far relatively few centres have contributed their data. Much of the information, as yet, is incomplete.

England and Wales

Fortunately, accurate information has been available for England and Wales for over 20 years from the publications of the Office of Population Censuses and Surveys. These indicate that in the last 10 years a precipitous decline occurred, of a degree which was never experienced in the past.

Concurrently, the selective non-treatment of the most severely affected has substantially decreased the number of profoundly handicapped survivors, which was such a prominent fate for many who were born in the 1960s.

In England and Wales the incidence of spina bifida was high, both absolutely and by international comparisons up to 1972. There were only minor fluctuations

in the rate which was on average 20 per 10,000 total births each year. In 1972, 1473 babies or 21 per 10,000 were born with spina bifida. This was the last year before antenatal diagnosis became a possibility.

Since then there has been a rapidly progressive decline in the births of spina bifida babies to 880 (14.9 per 10,000) in 1976 and to 422 (6.7 per 10,000) in 1983.

An even greater reduction occurred in anencephalic births from 13.1 per 10,000 total births in 1974 to only 1.8 in 1983. This substantial decrease can be largely accounted for by antenatal diagnosis followed by termination of pregnancy, although accurate figures for terminations are not available, as yet.

During the same period there was also a considerable decrease in the birth of hydrocephalic infants (unassociated with spina bifida) from 4.8 to 3.1 per 10,000, although antenatal diagnosis and terminations played no part in this decline. Possibly this is a true change in the incidence of the disorder and of similar degree to what might have been observed in the case of neural tube defects, had there been no medical interference. This suggestion is supported by the fact that in Ireland, where therapeutic abortions are not carried out, the incidence of spina bifida decreased to a similar proportion as is the case for hydrocephalus in England and Wales. Caution is necessary not to take the figures for hydrocephalus too literally, because many cases are not diagnosed in the neonate and so cases diagnosed later may not be included in the figures.

The exact role of antenatal diagnosis in the decrease of neural tube defects in the country as a whole is not fully clear: notifications of terminations of pregnancy because the foetus had a neural tube defect are almost certainly incomplete. Further, the official data merely give a total of terminations for *all* neural tube defects, without separating those for spina bifida and for anencephalus. With these provisos in mind, the figures indicate a rapidly increasing number from 34 in 1974 to a peak of 481 in 1980, but since then there has been no significant change in the notifications. As it is probable that most terminations were carried out because the foetus had anencephaly, the number terminated because of spina bifida was unlikely to have exceeded 150 in any one year, yet in 1982 some 1000 fewer babies were born with spina bifida than only 10 years earliers. The rate fell to on-third of the 1972 figure.

Selective terminations could, and should, play a bigger role in the prevention of spina bifida than was the case in the whole of England and Wales. This is shown for example by the experience in Sheffield in England, and Glasgow in Scotland.

Other congenital defects

Whatever are the cause, or causes, of the decline in CNS defects, these are not applicable to any other type of congenital malformations. On the contrary, the

prevalence of all congenital malformations, other than CNS defects, is on the increase. The rate for *all* congenital defects, including the CNS was 197 in 1974 and progressively increased to 221 per 10,000 total births in 1983. Excluding CNS defects the increase was from 159 to 209.

The experience in Sheffield

Sheffield is an industrial city with a population of 550,000 and an annual average of 6,500 births. An accurate congenital anomalies registry was established some 20 years ago, and it is a most valuable source of information. The information is abstracted from the birth certificates, on which every evident congenital abnormality is recorded.

Like elsewhere, there were no measures known to prevent spina bifida births until about 1965 [8] when my large scale study established that there was an approximate 5% risk of neural tube defects in a family after they had a baby with spina bifida. Prevention of recurrences, however, was only possible by avoiding further pregnancies. This made no measurable impact on the number of spina bifida births.

In 1972, after Brock's [1] first paper on the value of alphafetoprotein estimation in the amniotic fluid, it was in Sheffield in 1973 that the first termination was carried out because the foetus had an open neural tube defect. Since then, amniocentesis was offered to all high risk couples. Although this was most valuable to such couples, it made no measurable difference to the spina bifida births, because over 95% of such births are the first event in their families. Soon after came the possibility of discovering a much higher number of families at high risk with the estimation of the routine serum alphafetoprotein level in pregnant women and since then more and more „normal" pregnancies were monitored by serum tests. Routine serum tests started in January 1977 on women who presented at the antenatal clinic in good time and in 1983 over 90% of the pregnant population has been screened. When indicated, serum test was followed by amniocentesis.

Concurrently, increasing use was made of diagnostic ultrasound monitoring of pregnancies and now ultrasound monitoring of pregnancies is part of the routine management. The economic status of the city was improving in the 1960s. As the then Prime Minister, Sir Harold MacMillan, said "You've never had it so good." There was little unemployment and the diet of the population was probably as good as has ever been. Yet, the incidence of spina bifida was around 20 per 10,000 births. The late 1970s saw a progressive deterioration in the standard of living for those who became unemployed and by the 1980s some 15% of the population were jobless. It is not known wether this fact affected the nutrition of pregnant women.

During the 1970s and 1980s the annual *number* of spina bifida births fell progressively from an average of 18 in 1968–1970 to 10 in 1971–1973; 8 in 1974–1976; and 6 in 1977–1981. There were 2 in 1982 and 3 in 1983. The *rate* per 10,000 total births was 21 in 1968–1970 and only 4 per annum in 1982–1983. Further, in recent years a larger proportion than usual of these births had simple meningocele, so it was the more severe cases whose numbers declined most steeply. However, not all this decline was due to therapeutic terminations of pregnancy.

I carried out a detailed examination for 1979 to 1983 inclusive, of all the notifications of births; all the antenatal tests; and all the relevant obstetric records in the 3 large neonatal units where almost all births in Sheffield take place.

During these 5 years 8 babies were born with meningocele; 18 with myelomeningocele and 3 with encephalocele. In the same 5 years, 14 terminations were carried out because the foetus had myelomeningocele. Consequently, an average of 6 myelomeningocele *conceptions* occurred during these years which is about one-third compared with the experience in the 1960s but the number of *births* fell to an average of 3.6 per year. Antenatal diagnosis, therefore, reduced the number of such births by about 40%. The results are even more encouraging in 1982 and 1983. In these years there were only 4 myelomeningocele births and 9 terminations.

There are several reasons why there were still 18 births with myelomeningocele in the last 5 years. In 2 diagnosis was made antenatally but the parents refused termination; in a further 4 instances a suggestive positive serum result was not followed up by amniocentesis; and in another 4 instances the serum gave false negative results and ultrasound was not used. Finally, 8 were not screened, largely because the mothers attended too late for the first antenatal visit. In this group there was an undue proportion of immigrant women from the Asian subcontinent.

The problem of a large number of babies surviving with major multiple handicaps has been practically eliminated. There were only 18 babies born with myelomeningocele in the last 5 years, as compared with some 90 in 5 years in the 1960s. Thirteen of the 18 had severe permanently handicapping lesions at birth within the criteria for non-treatment. They were not treated and all 13 died early in infancy. Two others who were borderline cases were not treated at birth but were operated on later. These 2 and only these 2 are those who survived with severe handicaps. The last 3 were far less severe cases, were treated and survived with only mild to moderate handicap.

Antenatal screening was even more successful in contributing to the elimination of anencephalic births in Sheffield. No such births occurred in the last 3 years (1981–1983). During the same 3 years there were 15 terminations of anencephalic

foetuses. This comparses with an average of 13 such births per annum between 1968 and 1973.

If the currently available preventive measures were even more fully used, then the elimination of all myelomeningocele births becomes a practical possibility and the painful decision of selective non-treatment will hardly ever have to be used. The prospect would be even brighter if true prevention with adequate diet or vitamin supplementation of the entire pregnant population would prove to be of value and could be achieved by practical means.

Other English cities and Wales [10]

The general trend of decrease in the major cities in England was similar to that experienced in Sheffield. In 1983 the rate for 9 provincial cities with births of over 5000 in each was an average of 4.1, compared with the national average of 6.7. The only exception was *Bradford* (rate 8.7) which has a very large minority of Asian origin. In *Nottingham*, with 7657 births in 1983 not a single baby was notified of having been born with spina bifida.

This lower incidence in the cities must be balanced with the higher prevalence in smaller communities and suggests that the provision of antenatal services is better in the cities (where all the University units are located) than in rural areas.

The population of *"London"* is incorporated in to 4 different regions and includes large surrounding areas. In these 4 regions the rate was similar to the national average.

In *Wales* the incidence of spina bifida was always higher than in England. It still remains higher, but is falling fast. In 1983 37 babies were notified or 10.4 per 10,000 total births. This figure is now as low as in East Anglia. Interestingly, because East Anglia was a low incidence area, major efforts with routine antenatal tests were considered unnecessary [9]. The incidence is now higher there (10.3) than in any other English region.

Scotland

In the *West of Scotland*, with an average of 37,000 births a year, the major role played by antenatal diagnosis by serum alphafetoprotein tests was shown by Ferguson-Smith (1983) [5]. By 1981 73% of the pregnant population had routine serum tests; 1% only needed amniocentesis and 56 terminations of pregnancy were carried out where the foetus had spina bifida. Yet more cases of spina bifida were detected antenatally, but the mothers refused to agree to termination.

Greater Glasgow is within Western Scotland and is Scotland's largest city with an average of 13,000 births a year. Spina bifida births declined from 56 (40 per

10,000) in 1974 to only 10 in 1981 and to 7 (5 per 10,000) in 1983 [6]. Some 21 terminations were carried out in 1981 because of spina bifida, suggesting that 31 spina bifida conceptions took place, in contrast to the 56 7 years earlier. Terminations were responsible for about half of the decline in spina bifida births. Again, there must be additional explanations for the remainder of the six-fold reduction in a mere 7 years.

It is interesting that in Glasgow there was an equally rapid decrease in the births of babies with hydrocephalus unassociated with spina bifida from 16 in 1975 to 2 per 10,000 total births in 1983, although antenatal diagnosis and terminations for this condition were not practised [6].

Ireland

Ireland is divided into two countries: the smaller Northern Ireland, which is largely protestant and the larger Eire which is predominantly Roman Catholic. In both countries the incidence of neural tube defects, including spina bifida was always very high, possibly the highest in the world.

In *Northern Ireland* with an average of 30,000 births per year the annual rate of spina bifida births was 36 between 1964 and 1968 [3] and 33 between 1969 and 1973 [4], but in 1975 it even rose to 45 per 10,000 total births. Subsequently, a major drop occurred, down to 20 in 1980, about the same as was in England 10 years earlier.

In the capital, *Belfast*, the trend was similar but the rate was even higher, though by 1982 this dropped to 23. As only high risk women were offered antenatal tests, it is not surprising that according to Professor Nevin's estimate only 2% of this decrease can be attributed to selective abortions [9].

In *Eire* selective antenatal tests are rare and officially abortions are forbidden. Detailed birth statistics are available only for the capital, *Dublin*. Here the rate fell steeply from 32 in 1979 to 22 by 1982 but was still at least as high as it was in England & Wales or Sheffield in the 1960s. In contrast, the rate in Sheffield was 3 per 10,000 in 1982.

International data

Hungary

Detailed comprehensive national records are available from Hungary from the studies of Czeizel. Interestingly, the trend here is different to that seen in Great Britain. There was a steady decline in the incidence of spina bifida from 12 per 10,000 in 1970 to 7.5 in 1976[2], but then it started to rise again and there were 8.6 per 10,000 conceptions with a spina bifida foetus in 1982.

Antenatal diagnosis and termination of pregnancies on a small scale started in 1977. In 1982 spina bifida births were reduced, slightly, because of 9 selective terminations. It is not clear what proportion of the population are offered antenatal diagnosis but it is clear that the natural decline in Hungary has stopped and that, so far, selective abortions have made little impact on the birth incidence.

Even anencephalic births are only slightly on the decline.

The Federal Republic of Germany (Bundesrepublik Deutschland)

In the Bundesrepublik there is compulsory notification of congenital malformations detectable within the first 3 days of life. The results are published by the Statistisches Bundesamt in Wiesbaden, but it is probable that there is underreporting. A further source of error is that the figures do not include stillbirths. For example, in 1983 only 86 babies were reported to have been born with spina bifida, that is 1.4 per 10,000 births and only 12 liveborn with anencephalus. Yet, Koch and Fuhrmann [7] estimate that the current prevalence of NTD defects is about 10 to 15 per 10,000 births, with about equal distribution for spina bifida and anencephalus. The latter estimate, based on hospital statistics, is also liable to considerable error. Consequently, the regrettable conclusion is that there are no reliable data for the Bundesrepublik. Personal communications from various treatment centres and mortality statistics suggest, however, that there is a considerable recent decrease.

First-year deaths for the last 6 years, from 1978 to 1983 inclusive do indicate a substantial and year-by-year progressive decline from 114 in 1978 to 43 in 1983 (Statistisches Bundesamt, Wiesbaden). Methods of treatment are unlikely to have contributed to this decline, because during these years there have been no major changes in technique or in policies of selective treatment. Consequently, even if the data are incomplete, there are reasons to believe that the incidence of spina bifida in the Bundesrepublik is declining.

I could find no information, after extensive search, whether and to what extent are antenatal diagnosis and termination of pregnancy practised.

Other Countries

The International Clearinghouse for Birth Defects Monitoring Systems only provide data for 1980 to 1982 and so can give little firm idea, as yet, about the long term trends in the participating countries.

If the published figures are accurate, then within 3 years decreases of the order of 15–20% have taken place in *Czechoslovakia, Denmark* and *New Zealand*, none in *Finland* or *Norway,* while in *Hungary* and *Sweden* spina bifida may be on the increase.

Taking at their face value, the incidence in all the countries mentioned, except for Hungary, appear to be lower than in Great Britain even in 1982, but one is dubious whether the notifications are complete and whether the reporting is accurate. One can find widely differing figures relating to the same years for the same countries.

In the *United States* there are hospital-based statistics. Their birth defects monitoring programme records live and stillbirths based on 1,200 self-selected US hospitals and monitors some one million births yearly, this being approximately one-third of all births in the country. In 1970 – 1971 the rate per 10,000 births was 7.5, in 1976 – 1977 it was 5 and in 1980 it remained 5 [13]. Clearly, antenatal diagnosis has not made its impact yet in the United States but the overall incidence of spina bifida in the earlier years was much lower than in Great Britain. The gap had closed substantially by 1980.

From a small hospital-based statistics Stein and his colleagues from the Brooklyn Hospital, New York, were able to give a title to their paper "Is Myelomeningocele a Disappearing Disease?" [12].

Conclusion

In conclusion, in spite of the absence of reliable figures worldwide, and in spite of the different classifications used in various countries, there appears to be a general decline in the incidence of spina bifida which is particularly noticeable in the United Kingdom, possibly because it is easier to see a major decline in countries where the incidence was very high.

The total disappearance of spina bifida from much of the medically advanced and liberally-minded communities is now a real, none-too-distant possibility. Nevertheless, failure to use the existing and perhaps future preventive measures could lead to disaster and might still bring back conditions which existed in the past. We must be on guard against such events and not lull ourselves into false security, because just now spina bifida is on the decline for unknown epidemiological reasons.

Acknowledgements

1. Dr. A. Milford-Ward, Director of the Department of Immunology, The University of Sheffield, who carried out all the alphafetoprotein estimations and for allowing his records to be used for this paper.

2. Doctors Weatherhill and Alderson of the Office of Population Censuses and Surveys for valuable statistical information regarding England.

3. Dr. F. Hamilton and Mr. T. Sinclair of the Greater Glasgow Health Board who provided information for Scotland.

4. Dr. Proebsting of the Statistisches Bundesamt in Wiesbaden who provided information for West Germany.

5. Professor Ian Cooke of the University of Sheffield and Dr. B. A. M. Smith of the Northern General Hospital in Sheffield for valuable information regarding terminations and the outcome of pregnancies following antenatal tests.

6. The Richard Fund, Sheffield for secretarial assistance.

References

[1] Brock, D. J. H, R. G. Sutcliffe: Alphafetoprotein in the antenatal diagnosis of anencephaly and spina bifida. Lancet, 29th July (1972) 197 – 199.

[2] Czeizel, A.: Letter to British Medical Journal, vol. 287, 6th August (1983) 429.

[3] Elwood, J. H.: Major central nervous system malformations notified in Northern Ireland 1964 – 68. Dev. Med. and Child Neurol. **14** (1972) 731.

[4] Elwood, J. H.: Major central nervous system malformations notified in Northern Ireland 1969 – 73. Dev. Med. and Child Neurol. **18** (1976) 512 – 520.

[5] Ferguson-Smith, M. A.: The reduction of anencephalic and spina bifida births by maternal serum alphafetoprotein screening. Brit. Med. Bull., vol. 39, **4** (1983) 365 – 372.

[6] Hamilton, F. M. W., T. Sinclair: Greater Glasgow Health Board. Personal communciation (1984).

[7] Koch, M., W. Fuhrmann: Epidemiology of Neural Tube Defects in Germany. A review.

[8] Lorber, J.: The family history of spina bifida cystica. Pediatrics 35 (1965) 589.

[9] Nevin, N. C.: Prevention of neural tube defects in an area of high incidence. In: Prevention of spina bifida and other neural tube defects (J. Dobbing, ed.), pp. 127 – 144. Academic Press Inc., Ltd., London 1983.

[10] Office of Population Censuses and Surveys Monitor 1984 (*M3 84/5*).

[11] Standing, S. J., M. J. Brindle, A. P. MacDonald et al.: Maternal alphafetoprotein screening: 2 years' experience in a low-risk district. Br. Med. J., vol. 283, 12 September (1981) 705 – 707.

[12] Stein, S. C., J. G. Feldman, M. Friedlander et al: Is myelomeningocele a disappearing disease? Pediatrics, vol. 69, 5 (1982) 511 – 513.

[13] Winham, G. C., L. D. Edmonds: Current trends in the incidence of neural tube defects. Pediatrics, vol. 70, 3 (1982) 333 – 337.

In much of this paper references were obtained from the official statistics of the Office of Population Censuses and Surveys; the Sheffield Congenital Anomalies Register; the International Clearinghouse for Birth Defects Monitoring Systems; Eurocat and the Statistisches Bundesamt, Wiesbaden.

Comparative aspects of dysraphic malformations in domestic animals

M. Vandevelde

Dysraphic malformations such as anencephaly, encephalocoele, meningocoele and myelocoele, have all been described in most domestic and laboratory animals [2, 6, 7].

Spontaneously occurring malformations of the nervous system, have been closely studied in cattle with the primary purpose to decrease their incidence by breeding measures. The frequency of all malformations in this species is 0.3% of which one third also involve the nervous system. Spina bifida with or without neurospinal dysraphism is one of the most common congenital defects in calves. In most cases, spina bifida is associated with other CNS anomalies especially the Arnold Chiari malformation. Another frequent combination is spina bifida, neurospinal dysraphism and articular rigidity also known as the bovine congenital arthrogryposis syndrome. Extensive teratologic studies on large numbers of newborn calves suggest that genetic factors play an important role in the pathogenesis. These results were based on systematic analysis of the offspring from parental animals used for artificial insemination [19]. Although some parental animals have a much higher malformation frequency in their offspring than others, the genetic mechanism is difficult to explain in most cases because calves often exhibit multiple, apparently unrelated malformations. Therefore the concept of genetic burden is applied: by exceeding a certain critical number of deletary cooperating genes in the population, malformations occur. Environmental factors, especially infectious agents can not be excluded as possible causes. However, although many viruses are known to produce development defects in the CNS of domestic animals ranging from hydrocephalus to deficient myelin development, infectious agents specifically causing dysraphic malformations have not been identified.

In companion animals (dogs, cats) dysraphic malformations have been described mostly as sporadic cases [3, 4, 8, 10]. Spina bifida and associated cord malformations are the most common defect. In contrast to cattle these lesions in small animals are usually not combined with other malformations. The most common site is the lumbosacral area with bladder, colon and sphincter problems but rarely locomotor signs. Spina bifida in dogs has a very high incidence in the English Bulldog which would suggest genetic factors.

Reproducible hereditary neural tube defects have been studied in the Manx cat and the Weimaraner dog. The dysraphic malformation in Manx cats is genetically associated with the absence of the tail, including sacrococcygeal dysgenesis, spina bifida with or without meningo-myelocoele and incomplete development of the sacral spinal cord and cauda equina. α-feto-protein has been demonstrated in the amniotic fluid of Manx cats with neural tube defects. The mode of inheritance is autosomal dominant with incomplete penetration.

Neurospinal dysraphism in Weimaraner dogs is clinically characterized by a hopping gait; other, less common, signs are thoracolumbar scoliosis, koilosternia and abnormal hair streams in the cervical area. In all clinically affected animals more or less subtle spinal cord malformations may be found at all levels and include: lack of a dorsal septum; absent, enlarged or abnormally shaped central canal; abnormal position and fusion of the ventral horns; absent or incompletely penetrating ventral median fissure. In adult dysraphic Weimaraner dogs syringomyelia, especially in the central areas and along the dorsal midline is common.

Neurospinal dysraphism in Weimaraner dogs has a partially dominant mode of inheritance with incomplete penetration and variable expression. By mating clinically dysraphic animals 70 – 80% of the embryos or fetuses exhibit spinal cord anomalies. True closure defects of the neural tube have not been observed in developmental studies; abnormal migration patterns appear to be the underlying defect whereby parts of the mantle layer are displaced ventrally and invagination of the ependyma appears to result in a duplication of the caudal neural tube.

References

[1] Cho, D. Y., H. W. Leipold: Spina bifida and spinal dysraphism in calves. Zbl. Vet. Med. A, **24** (1977) 680 – 695.

[2] Done, J. T.: Developmental disorders of the nervous system in animals. Adv. Vet. Sci. and comp. Med. Academic Press, New York, San Francisco, London, vol. 20 (1976) 69 – 114.

[3] Engel, H. N., D. D. Draper: Comparative prenatal development of the spinal cord in normal and dysraphic dogs: embryonic stage. Am. J. Vet. Res. **43** (1982) 1729 – 1734.

[4] Engel, H. N., D. D. Draper: Comparative prenatal development of the spinal cord in normal and dysraphic dogs: fetal stage. Am J. Vet. Res. **43** (1982) 1735 – 1743.

[5] Herzog, A.: Embryonale Entwicklungsstörungen des Zentralnervensystems beim Rind. Habilitationsschrift, Gießen 1971.

[6] Kalter, H.: Teratology of the central nervous system. The University of Chicago Press, Chicago – London 1968.

[7] Kitchen, H.: Spina bifida. In: Spontaneous animal models of human disease. Vol. II. (E. J. Andrews, B. C. Ward, N. H. Altman, eds.). Academic Press, New York – London – Toronto – Sydney – San Francisco 1979.

[8] McGrath, J. T.: Spinal dysraphism in the dog. Pathologia Veterinaria, vol. 2, Suppl. S. Karger, Basel – New York 1965.
[9] Rieck, G. W., A. Herzog, W. Schade: Modell Hessen: Populationsweites Kontrollsystem zur pathologischen Überwachung des Besamungsbullen. Tierärztl. Umschau **6** (1977) 305 – 314.
[10] Wilson, J. W., H. J. Kurtz, H. W. Leipold et al.: Spina bifida in the dog. Vet. Pathol. **16** (1979) 165 – 179.
[11] Frauchiger E., R. Fankhauser: Vergleichende Neuropathologie des Menschen und der Tiere. Springer Verlag, Berlin 1957.

The embryology and pathology of dysraphias

U. Roessmann

Following the gastrulation phase, the cells of the dorsal region are induced through the chordomesoderm to form the neural plate. This neuroepithelium, which is to form the central nervous system proliferates and expands into the neural groove. The fusion of the dorsal rims of the neural groove – neurulation – begins approximately 20 days after the fertilization of the ovum. Failure of closure or its disruption after it has closed are presumed to be the basic events in the formation of the dysraphic malformations.

Myelomeningocele is the prototype of the schisis of the neural tube. The spinal cord is formed as if the neural groove never closed and the cells simply matured in the normal sequence. The neural arch above remains open and the attached muscular structures are poorly, if at all, developed. In most instances the entire lesion is covered by a layer of very simply structured epidermis. This sequence can be considered as a primary failure of induction to close the neural tube, which in turn fails to induce the formation of mesenchymal elements. Since the caudal neuropore is the last site to close, it seems natural that its failure to close should lead to the most commonly occurring lesion. There is, however, evidence that the involved segments of the spinal cord in the lumbo-sacral region are formed only after the caudal neuropore has already closed. They arise from the so-called end-bud through coalescence and canalization of several proliferating cell groups [5]. Since the end-bud organization is a much more complex event than the actual neuropore closure, it is somewhat easier to think in terms of improper induction through the closely involved chordal tissue rather than of failure of closure or reopening of the already closed tube. In the majority of the surgical specimens following the repair of the myelomeningocele, the neural elements consist primarily of disorganized islets rather than exhibiting the classical open cord picture. This suggests that the neuroepithelial tissue in the most involved area never reached the neural groove stage of organization.

In contrast, true dysraphic spinal cord is usually found at higher levels. The lesion consists of a bifid spine and a well organized but split spinal cord, which are enclosed by normal subcutaneous tissue and covered by intact skin. The rachischisis fails to induce the disruption of the overlying skin and muscle. The most logical explanation for such a lesion is that the neural groove develops normally but fails to close and that it secondarily induces the vertebral anomaly. Presumably, the spinal cord in such lesions should be structurally and functionally

intact, save for the split. Such a presumption, however, must not be accepted without further evaluation, both through more exact anatomical observations as well as through physiological studies. With new diagnostic capabilities it should be possible to identify individuals with such lesions that may be minimally symptomatic and study the physiological parameters of the split spinal cord. No observations from such cases are available at present on the segmental organization of the spinal cord or on the skeletal muscle in the involved region, although Barson [1] has emphasized that a kyphosis does not occur with the lesions above low thoraco-lumbar levels. Furthermore, such lesions may be associated with symptoms related to lower segments which still need explaining.

Another interesting problem is the longitudinal splitting of the spinal cord which may or may not be associated with skeletal malformations. These changes are described under the names of diplomyelia or diastematomyelia. The two terms used are interchangeable in the literature. Confusion could be avoided by use of words such as duplication and splitting (Verdoppelung or Spaltung). The split cord is of considerable clinical interest since the frequent presence of a dural septum containing bony or cartilagenous spicules interferes with the proper relationship between the neural elements and the vertebral column during the development, particularly during the rapid growth phase of the adolescent. This misalignment results in stretching of the spinal cord and of the rootlets, causing symptoms and requiring surgical intervention. The doubled spinal cord is of more interest to the physiologist who would like to know the functional aspects of this abnormality. From an anatomical point of view the two malformations are most confusing because of the lack of the distinguishing criteria and the multiple overlapping aspects of the anatomical findings. From an embryological viewpoint the cause of this remains unclear. To explain the split cord, Bremer [2] has postulated a persistent neurenteric canal as the basic pathogenetic mechanism. The dorsal fistula should result, in an anterior division of the neural tube. It is not possible, however, to find such a neurenteric canal or an anterior vertebral defect in every case of diastematomyelia or diplomyelia. Furthermore, there are so many problems of overlapping between these malformations and the failure of the closure type of malformations that it is difficult to envisage a single pathogenetic mechanism for the entire group. We have examined a case in which duplication of the spinal cord occurred together with the duplication of the pituitary gland. Since the neurulation and the development of the hypophyseal anlage take place at approximately the same time and, since both probably are induced by the chordomesenchymal tissue, it seems reasonable to suggest that such malformations can occur under the perturbed influence of the notochord. There is experimental evidence available to support the view that notochordal disturbance induces proliferation of the cells in the neural plate which could result in duplication.

Anencephaly is the most frequent dysraphia, but because of its lethal outcome it is of no interest to neurosurgeons. Because of its peculiar geographic and ethnographic distribution it has initiated epidemiological studies searching for a causative agent. Anatomically, the most significant findings are those of Marin-Padilla [6], who demonstrated convincingly that the skeletal malformation is an integral part of the problem. While it is again not possible to say which structure induces the other, it seems clear that the extent of the brain destruction depends on the extent of the bony defect. It is not possible to explain the entire complex with a simple failure of closure of the anterior neuropore. It is more likely, that the failure of the mesenchymal tissue elements results in the destruction of the more or less normally induced neural components which have reached a fairly advanced state of organization. This is shown by the development of the eyes and other parts of the system which remain preserved in such cases where the bony defect allows it. The problem of exencephaly seems to contradict this idea, yet careful examination actually support it. The exencephalic brain shows no evidence of any failure of closure. The changes seen in such brains are more consistent with interference with the cell multiplication. This occur at considerable time after the neuropore closure, and are most likely due to external factors acting on the growing brain in the absence of the protective skeleton.

The Chiari complex is of greatest interest to the clinical branches. It is most amenable to corrective measures and even offers possibilities for intrauterine treatment, but it presents a most confusing problem due to its anatomical complexity. This malformation has at least two components, which at first sight seem to differ in their embryological derivation. The first is myelomeningocele, most commonly in the lumbo-sacral area, which was discussed above. The second component consists of the major malformation at the foramen magnum. Here, instead of the neural tube defect, there is a massive caudal displacement of the structures of the brain stem. Not only is there a shift in relation to the surrounding bones, but also between the ventral and dorsal components of the brain stem, further complicated by the involvement of the cerebellar structures. All theories to explain these complex events on purely mechanistic grounds are clearly inadequate. The first study to use an embryological approach is that of Jennings et al. [4]. The authors propose a downward displacement of the brain-cord transition zone during the initial fusion of the neural folds. This could result in a displacement of the "anlage" forming the caudal rhombencephalon and of the somites programmed to develop the cervical vertebrae. While there may be missing parts in the story, the proposal has considerable merit in providing a unified explanation for the entire complex. A downward shift in the brain-cord transition zone could also result in a downward shift in the induction of the remainder of the neural tube leading to the schisis in the lumbo-sacral area.

The severity of the shift may also vary, resulting in variations in the extent of the malformation in the posterior fossa and foramen magnum region. This variation results in clinically less severe problems and allows for a variety of symptom complexes. To alleviate confusion in the nomenclature a simplified classification is proposed [3]. It is based on decreasing severity of the anatomical malformation and correlates with the clinical course of the patients. In the adult the Chiari malformation is characterized by survival before the symptoms become manifest and anatomically consists of a downward herniation of the cerebellar tonsils, the medulla oblongata and the fourth ventricle. Chronic tonsillar herniation is a self-defining term. In both groups the spinal dysraphism is virtually non-existent, but in both instances segmental malformation of the cervical spine, cervico-occipital misalignment and syringomyelia frequently occur. Both groups are of great clinical interest since they respond well to simple posterior fossa decompression.

References

[1] Barson, A. J.: Spina bifida: The significance of the level and extent of the defect to the morphogenesis. Dev. Med. Child Neurol. **12** (1970) 129 – 144.

[2] Bremer, J. L.: Dorsal intestinal fistula; Accessory neurenteric canal; Diastematomyelia. Arch. Pathol. **54** (1952) 132 – 138.

[3] Friede, R. L., U. Roessmann: Chronic tonsillar herniation. An attempt at classifying chronic herniations at the foramen magnum. Acta Neuropathol. (Berl.) **34** (1976) 219 – 235.

[4] Jennings, M. T., S. K. Clarren, V. G. Kokich et al.: Neuroanatomic examination of spina bifida aperta and the Arnold-Chiari malformation in a 130-day human fetus. J. Neurol. Sci. **54** (1982) 325 – 338.

[5] Lemire, R. J.: Variations in development of the caudal neural tube in human embryos (Horizons XIV to XXI). Teratology **2** (1969) 361 – 370.

[6] Marin-Padilla, M.: Morphogenesis of anencephaly and related malformations. Curr. Top. Pathol. **51** (1970) 145 – 174.

Neural tube defects: Experimental findings and concepts of pathogenesis

R. C. Janzer

Introduction

It is generally accepted that the aetiology and pathogenesis of neural tube defects (NTD) are multifactorial. They include genetic predisposition as well as environmental factors [1, 12]. A recent advance in prophylaxis has been achieved by the clinical finding that periconceptional administration of multivitamins, especially folic acid, can significantly reduce recurrences of NTD [10, 24]. Despite this progress the basic mechanisms leading to NTD remain for the most part hypothetical. For testing concepts of pathogenesis the use of animal models and substances with known sites of action are essential. Of the more than 30 agents known to produce dysraphic lesions [3] most are effective only around the restricted time of fusion of the neural folds [9]. Therefore, the most probable common mode of action of several teratogenic agents lies in the disturbance of cell adhesion and recognition mechanisms during neural fold fusion. Glycosylated membrane proteins and lipids are generally known to play an important role in these mechanisms [2, 6]. We therefore investigated the normal distribution of Concanavalin A binding sites during neurulation in the chick embryo by light-, scanning- and transmission-electron-microscopy and induced NTD by topical application of Concanavalin A.

Material and methods

A more detailed description of the methods employed is given elsewhere [8]. Briefly, stage 6 to 10 chick embryos [5] were divided in two main groups. Group A (for investigation of normal distribution of Concanavalin A binding sites) was either fixed in 2% glutaraldehyde, exposed to ferritin-conjugated Concanavalin A and processed for scanning or transmission electron microscopy (SEM and TEM), or treated first with FITC-conjugated Concanavalin A, freeze-dried and examined by fluorescence microscopy. In controls, Concanavalin A (Con A) was replaced by Ringer's solution. Group B (for induction of NTD) was treated in ovo by a single subgerminal injection of native Con A (or Ringer's solution in

controls). After various time intervals the embryos were fixed in 2% glutaraldehyde and processed for SEM or TEM. The processing for SEM was the same for both groups A and B. The specimens were glued onto a stainless steal grid and the whole preparation either postfixed in OsO_4 or 2% glutaraldehyde. After dehydration in acetone and critical-point-drying in liquid CO_2 the specimens were mounted onto object holders. A gold coating was applied in a sputtering device. After SEM-examination the specimens were transfered to ethanol, embedded in araldite and further processed according to standard TEM procedures. The ultrastructure of specimens previously processed for SEM was comparable to that of embryos processed directly for TEM.

Results

Normal distribution of Concanavalin A binding sites

The normal distribution of Con A binding sites, described elsewhere in more detail [7], showed a predilection for the leading edges of the neural folds prior to fusion. The greatest amount of binding sites was seen on a few cell layers of the opposing neural folds in the fusion zone. At the luminal surface of the basal portion of the closing neural tube there was only weak staining. This pattern could be similarly observed in the fusion zone of stages 7, 8, 9 and 10. Older stages were not investigated. Rostrally and caudally from the fusion zone significant amounts of Con A binding sites were observed at the edges of the elevating neural folds but were not found in the adjacent neural groove or lateral surface ectoderm.

Dysraphic lesions induced by Concanavalin A

Dysraphic lesions in the cervico-thoracic region were obtained in about 40% of the animals treated by subgerminal injections of Con A. Twentyfour hours after treatment the extent of the dysraphic lesion was greatly variable. Small lesions measured about 200 microns while larger ones occupied the whole length of the cervico-thoracal spinal cord (fig. 1A, 1B). The lumbosacral region was not affected in any of these animals. The dysraphic lesion was covered cranially and caudally by normal ectoderm. Specific changes were seen at the lateral edges of the open neural tube selectively at the junction between neural folds and lateral ectoderm at the level of the dysraphic lesion. These changes consisted of malorientated filopodia and excessive blebbing (fig. 2B). Blebs consisted of rounded cells or cell portions attached by intermediate type cell junctions to the underlying