# GENETIC STUDIES OF ACUTE WERDNIG-HOFFMANN DISEASE

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*A large genetic survey of all infantile and childhood spinal muscular atrophies has been undertaken. Two large series have been studied, one consecutive series of 160 patients presenting to the Hospital for Sick Children, London, and approximately 60 patients from the Muscular-Dystrophy-Group Research Laboratories, Regional Neurological Centre.*
*Using the techniques of sibling-sibling correlation it has been shown for the first time that the acute fatal infantile form (classical acute Werdnig-Hoffmann disease) is a distinct genetic entity. It is then possible by such genetic techniques to define accurately the clinical syndrome.*
*Implications for genetic counselling are discussed. Gene frequency studies have been undertaken from this research project and it is now known that the carrier rate for the acute Werdnig-Hoffman disease gene is in the range 1:60 to 1:90 in the British population.*

There has been considerable discussion in recent years whether acute infantile spinal muscular atrophy (Type 1 SMA, Emery 1971) is a distinct clinical and genetic entity. Many workers, particularly clinicians encountering children of all ages with spinal muscular atrophy, have considered SMA to comprise a single disease with a broad clinical spectrum. Other workers, particularly geneticists, have been struck by the frequency with which affected siblings show striking clinical resemblance. The great majority of cases of SMA are transmitted as autosomal recessives, and it is important, for the subjective interpretation of the 1:4 recurrence risk involved, to have some idea of the likely clinical outcome of an affected child if such is subsequently born (Pearn 1973). In addition the clinical management of an affected child depends so much on knowing the natural history of the specific disease from which he suffers. For this reason a genetic study was undertaken to answer the question, is acute infantile SMA (Type 1) a distinct clinical and genetic entity?

To answer this question the technique of sib-sib correlation (Haldane 1941) has been used. This valuable technique has been used to demonstrate objectively the genetic heterogeneity of some other neurogenetic conditions (Brackenridge 1972, Bundey and Carter 1972).

All children of all ages with spinal muscular atrophy presenting to two large hospitals in England were studied. All children presenting to the Hospital for Sick Children, London, and to the Regional Neurological Centre, Newcastle upon Tyne, in the decade 1961-1970, were considered (See Table 1). Age of onset of the disease, age when they were first taken to the doctor because of parental concern, and age of death, were documented in each case.

Full genetic kindreds were also taken from each family. A total of 215 families have been personally investigated. For the sib-sib analysis families were excluded if a parent was similarly affected (these kindreds being assumed to manifest dominant spinal muscular atrophy which has different clinical features), if the disease clinically was of the form known as distal spinal muscular atrophy or the neurogenic form of the scapulo-peroneal syndrome. Of remaining families, 53 had two or more sibs affected, and these were used for the sib-sib analysis.

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TABLE 1

CASE-FINDING DATA FOR THE SIB-SIB CORRELATION ANALYSIS

[*The Hospital for Sick Children, London, and the Regional Neurological Centre, Newcastle upon Tyne*]

| | |
|---|---|
| Number of index patients | 215 |
| Number of families with 2 or more affected sibs | 53 |
| Numbers of sib pairs | 58 |

Using the sib-sib correlation technique it has been shown that the acute fatal infantile form of SMA is a distinct familial entity (see Tables 2 and 3). Its important clinical features are: (*a*) it is almost always clinically manifest by 3 months of age; (*b*) affected children are always taken to their doctors in England by 6 months of age, and this is in effect " a milestone " of the disease; and (*c*) affected children do not in my experience survive beyond the age of 30 months with this condition.

TABLE 2

CORRELATION COEFFICIENTS OF CLINICAL DATA OF ALL SIB PAIRS WITH SPINAL MUSCULAR ATROPHY (N = 58 pairs)

| | Correlation coefficient | 95% confidence limits |
|---|---|---|
| Age at clinical onset | 0.80 | 0.66-0.90 |
| Age when child first taken to doctor | 0.78 | 0.59-0.88 |

TABLE 3

CORRELATION COEFFICIENTS OF THE CLINICAL DATA ON THE SIB PAIRS CONCORDANT FOR ACUTE WERDIG-HOFFMANN DISEASE. (N = 30 pairs)

| | Correlation coefficient | 95% confidence limits |
|---|---|---|
| Age at onset before 3 months | 0.48 | 0.09-0.75 |
| Age at death | 0.47 | 0.06-0.68 |

Beevor (1902) first recorded that pregnant mothers carrying an affected child may experience subjectively reduced foetal movements in the third trimester. This phenomenon has been studied and a minimum of 30% of mothers experience this phenomenon (Pearn 1973). Unfortunately this assessment is far too imprecise and occurs far too late in pregnancy for it to be considered in the context of genetic prenatal diagnosis.

Less than 2% of affected children are ever able to sit unsupported and 30% only were able to lift their heads (even momentarily) from the bed at any time during life.

TABLE 4

INCIDENCE OF ACUTE SPINAL MUSCULAR ATROPHY TYPE 1 IN NORTH-EAST ENGLAND

| County | Total live births | Index cases of acute WHD |
|---|---|---|
| Northumberland | 50,922 | 1 |
| Newcastle upon Tyne | 21,549 | 0 |
| Durham | 158,899 | 8 |
| Total | 231,370 | 9 |

TABLE 5

GENE AND CARRIER FREQUENCY OF SPINAL MUSCULAR ATROPHY TYPE (ACUTE WERDNIG-HOFFMANN DISEASE)

| | |
|---|---|
| Incidence | 1 in 25,708 live births |
| Carrier frequency | 1 in 80 |
| Gene frequency | 1 in 160 ($q = 0.0063$) |

The gene and carrier frequency of this condition has also been assessed. There exists in the North-East of England a neuromuscular clinical and research centre of international reputation. Children affected by this condition in the North-East of England tend to be taken to this centre for diagnosis and management or are at least known to the centre with its extensive clinical and research facilities. For this reason one has been able to undertake a total population survey of all cases diagnosed in the region (Tables 4 and 5). This study has shown that the carrier frequency for the English population is approximately 1 in 80, a finding consistent with earlier impressions (Carter 1972) that this disease is the second or third most common fatal recessive disease of childhood.

## REFERENCES

Beevor C.E. 1902. A case of congenital spinal muscular atrophy (family type), and a case of haemorrhage into the spinal cord at birth, giving similar symptoms. Brain, 25: 85-108.

Brackenridge C.J. 1972. Familial correlations for age at onset and age at death in Huntington's disease. J. Med. Genet., 9: 23-32.

Bundey S., Carter C.O. 1972. Genetic heterogeneity for dystrophia myotonica. J. Med. Genet., 9: 311-315.

Carter C.O. 1972. Director, M.R.C. Clinical Genetics Unit, The Institute of Child Health, London. Personal communication.

Emery A.E.H. 1971. Review: The nosology of the spinal muscular atrophies. J. Med. Genet., 8: 481-495.

Haldane J.B.S. 1941. The relative importance of principal and modifying genes in determining some human diseases. J. Genet., 41: 149-157.

Pearn J.H. 1973. Fetal movements and Werdnig-Hoffmann disease. J. Neurol. Sci., 18: 373-379.

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