Acute Werdnig-Hoffmann disease

Acute infantile spinal muscular atrophy

J. H. PEARN and J. WILSON

*From the MRC Clinical Genetics Unit, Institute of Child Health; and
The Hospital for Sick Children, Great Ormond Street, London*

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Acute Werdnig-Hoffmann disease: acute infantile spinal muscular atrophy. 76 cases of acute Werdnig-Hoffmann disease (acute infantile spinal muscular atrophy) have been reviewed. The cases comprise an unselected consecutive series in which rigid diagnostic criteria have been applied. The natural history of the disease has been investigated. In at least one-third of cases the disease is manifest before or at delivery. All cases have shown delayed milestones by 5 months of age: 95% are dead by 18 months. Cumulative frequency curves for age at onset and age at death figures are presented for use both as prognostic guidelines and as aids in the management of sibs of index cases. Diagnosis, management, and genetic implications are discussed.

Acute Werdnig-Hoffmann disease (Type I spinal muscular atrophy; Emery, 1971) results from a genetically determined progressive degeneration of anterior spinal neurones. The disease is the second or third most common fatal recessive disease of childhood in Britain (C. O. Carter, personal communication, 1972).

It has been recently shown that acute Werdnig-Hoffmann disease is a distinct genetic entity whose clinical manifestations overlap, but are distinguishable from, those of the chronic forms of childhood spinal muscular atrophy (Pearn, Carter, and Wilson, 1973). Such a distinction of the acute disease has been shown to be possible using the genetic techniques of sib analysis. Using such genetic techniques to measure intrafamilial variation, it has become possible to define provisionally clinical boundaries of this acute genetic disease for the first time. In our consecutive series of all cases of childhood spinal muscular atrophy (both acute and chronic), we have been able to show that individuals with the *acute* form of the disease are inevitably dead by 3 years of age. It is now over 20 years since Brandt's (1950) extensive monograph on this disease was published. Since that time the pathology of the disease has been further elucidated (Byers and Banker, 1961; Huttenlocher and Cohen, 1966; Malamud, 1968; Nieves and Castello, 1970;

Chou and Fakadej, 1971), and the differential diagnosis has been extended by the recognition and more exact definition of diseases which may be clinically similar (Walton, 1956, 1957; Byers and Banker, 1961; Dubowitz, 1964; Rabe, 1964; Spiro, Shy, and Gonatas, 1966; Bethlem *et al.*, 1969; Duncan *et al.*, 1970; Wilson, 1970).

During the course of a larger study we have reviewed the case histories of 76 children with this disease and have interviewed personally 66 of their parents.

Methods

Cases. The 76 cases were drawn from a consecutive series of children with all forms of spinal muscular atrophy who presented at The Hospital for Sick Children between 1961 and 1970, inclusive. All infants diagnosed as Werdnig-Hoffmann disease, amyotonia congenita, Oppenheim's disease, spinal muscular atrophy, or benign congenital hypotonia were considered for review. Cases were excluded if (a) electromyography had not been performed, (b) if the electromyogram was not compatible with motor neurone degeneration, (c) if nerve conduction times were abnormal, (d) if CSF protein was abnormal, (e) if the child had survived for 3 years or longer. These latter were considered to have a chronic form of the disease (Pearn *et al.*, 1973). Cases in which a biopsy had been performed and which did not show the typical features of neurogenic muscular atrophy were also excluded. Of the 76 cases remaining in the study, 64 had had a confirmatory histological examination of muscle tissue

at some stage of the disease. Most cases had been subjected to lumbar puncture and most had had serum creatine phosphokinase estimations performed. 4 families declined to co-operate, but some reliable data (age at death, etc.) were obtained from records in these cases.

Interviews. In all but 6 cases the parents were interviewed personally. In these latter cases interview was by mail questionnaire as the family had moved overseas or lived too far away to be easily visited.

Information. One of us (J.W.) has been responsible for the clinical management of 15 of the cases. Documented details of pregnancy, labour, and early symptoms were obtained from source records in 75% of the cases and were checked against information given by the parents. In every case clinical details of presenting signs, investigations, management, progress, and outcome were available.

At interview with the parents details of all developmental milestones, presenting symptoms, and parents' concepts of the disease were obtained, and full pedigree studies undertaken. Norms for different developmental milestones were taken from Griffiths (1954), Bayley (1969), and Neligan and Prudham (1969). The disease was considered to be clinically manifest (a) when the normal age for the 95th centile had been passed for a specific motor skill, (b) when the infant was initially taken for medical advice, (c) if a doctor independently recognized and recorded significant hypotonia, e.g. in the nursery, or (d) if a significant orthopaedic abnormality was present at birth in an infant subsequently shown to have been affected.

Results

The frequency of congenital abnormalities noted at birth is shown in Table I. These are attributable to synergist-antagonist imbalance. In the earlier stages of the disease at least, asymmetry of affected muscle groups is often a feature; it is not surprising that even among different muscle groups of the same limb there is sufficient imbalance to produce orthopaedic deformity.

TABLE I

Incidence of abnormalities noted at birth and attributable to synergist-antagonist imbalance. 9 cases out of a series of 76 with acute Werdnig-Hoffmann disease

Congenital abnormality	No. of cases
Bilateral wrist deformity	2
Unilateral wrist deformity	2
Orthopaedic abnormalities, hands and feet	1
Chest asymmetry	3
Bilateral dislocated radial heads*	1

*Abnormality of forearms noted at birth and shown radiologically after 4 months.

The reasons for which parents initially sought medical advice are shown in Table II. Generalized weakness and hypotonia (Fig. 1) and feeding difficulties account for 61% of initial presentations. In severely affected infants oral feeds often took 90 minutes or longer and most infants required tube feeding for varying periods before death. Two mothers first sought medical advice specifically because of gross muscle fasciculation.

TABLE II

Relative frequency of presenting symptoms and signs in acute Werdnig-Hoffmann disease (data from 59 cases)

Weak movements, floppiness	37
Weak, poor, or prolonged feeding	24
Failure to progress to specific motor milestones	14
Diagnosis while in postnatal nursery or independently by doctor	14
Combination of orthopaedic deformity and weakness	4
'Unusual breathing': usually rapid and diaphragmatic	3
Other	4

The ages of clinical manifestation of the disease are shown in Fig. 2. It can be seen that reduced fetal movements or orthopaedic deformity present at birth imply that a minimum of one-third of cases had a prenatal onset. In families in which a previous child had died from acute Werdnig-Hoffmann disease the parents were naturally more alert to the early physical features of the disease. When questioned retrospectively many said they recognized the first signs much earlier in a second or subsequently affected sib. Analysis of our results shows, however, that a second affected

FIG. 1.—Female patient, age 4 months, with acute spinal muscular atrophy. Profound hypotonia and weakness are the most striking signs in this disease.

FIG. 2.—Times of appearance of clinical signs in acute Werdnig-Hoffmann disease. Cumulative frequency curve for age at onset of clinical signs, particularly delayed motor milestones. Data from 72 cases. It can be seen that in at least 95% of cases the child had manifested signs of the disease by 4 months of age.

child was taken to the doctor only marginally earlier in general, though exceptions occurred. Some parents volunteered the information that in the case of a second affected child they continued to ignore signs of weakness and to hold forlorn hope that all was well, even in the face of overt evidence to the contrary.

The information in Fig. 2 is presented in the form of a cumulative frequency curve. In this form it can be used in the practical management of an infant born to parents genetically at risk, that is, parents who have shown their genetic status (i.e. heterozygotes) by having had a previously affected child. In such cases, if a sib is born subsequently, it can be seen by reference to Fig. 2 that if, for example, the infant is still normal by 4 months, then he has passed 95% of his risk period and reassurance can reasonably be given.

Life expectancy is shown in Fig. 3 in both histogram and cumulative frequency forms. It can be seen that at least 95% of children are dead by 18 months, with a mean life expectancy from birth of 5.9 months and a median of 7 months.

We thought it valuable to inquire about parents' knowledge of the implications of the disease. Such a study provided some unique feed-back about the way parents reacted to a tragic human and genetic situation (Table III). Most parents

FIG. 3.—(a) Histogram showing age at death of 78 children with acute Werdnig-Hoffmann disease. Consecutive unselected series. (b) Cumulative frequency curve from data in (a), 50th and 95th centiles are indicated.

(a minimum of 70%) in this series had been told of the recurrence risk. It can be seen that only a minority (38%) admitted knowing recurrence risks. We interpret this as further evidence for the generally held view that such bad news tends to be rejected subconsciously as part of the complex psychodynamic response of parents who find themselves in this situation. Genetic counselling must be offered at the right time and presented in the

TABLE III

Degree of parental understanding of nature of child's illness in 42 families with 1 or more children with acute Werdnig-Hoffmann disease

Parent group	%
No idea of genetic nature of disease	33
Knowledge of genetic association but none of recurrence risks	29
Knowledge of recurrence risk of 1 in 4	26
Complete knowledge of nature of disease and recurrence risks	12

right way if parents are to assimilate it (C. O. Carter, personal communication, 1972).

Discussion

Electronmicroscopical evidence suggests that the neuronal abnormality may start as early as the 4th month of fetal life (Chou and Fakadej, 1971). Fetal movements are quantitatively reduced and qualitatively abnormal in over one-third of affected pregnancies. Otherwise, pregnancy is usually unremarkable except in those cases in which a mother has already borne a child who has developed acute Werdnig-Hoffmann disease. The pregnancy of many such mothers is naturally overshadowed by knowledge of the high recurrence risk (1 in 4) involved. In the case of pregnant mothers who are known to be genetically at risk it is important that a paediatrician be involved before the birth.

Labour itself is not modified by the presence of fetal Werdnig-Hoffmann disease, but delivery results in 5% of affected neonates manifesting birth trauma, usually brachial plexus lesions or dislocations. These latter probably result from fetal hypotonia. Congenital abnormalities due to prenatal onset of the disease are also significant (see Table I), a phenomenon recognized for over 50 years (Reuben, 1917). If a woman has had a previously affected child by the same father, and if pregnancy has been marked by reduced fetal movements, the appearance at birth of hand, wrist, or chest deformity is virtually diagnostic of the disease.

A common observation at the delivery of an affected babe was the failure to establish a lusty cry often associated with prolonged cyanosis; resuscitation difficulties with a hypotonic neonate must be anticipated in the case of a pregnant woman genetically at risk.

The central clinical theme of the disease is that of severe progressive hypotonia and paralysis (Fig. 1) set against a background of normal intellectual development. The reasons for which a doctor was initially consulted (Table II) illustrate the global effects of the hypotonia. Motor milestones are universally delayed. Only 1 of the 76 cases was ever able to sit unsupported and only 20 (27%) were able to lift the head (even momentarily) from the bed at any time during life. One valuable inquiry was to ask about the ability to kick off the bedclothes as normal infants do, but norms for this milestone are not available. The faces of affected infants show a characteristic immobile expression and are often 'devoid of all lines which give individuality' (Reuben, 1917). As in all forms of spinal muscular atrophy, the lower limbs

are affected earlier and more severely than the upper.

The differential diagnosis includes all causes of the 'floppy infant', but we have found that the gross weakness and whole clinical picture is very distinctive. Global paresis as opposed to hypotonia has been stressed by Dubowitz (1968). Occasionally conditions such as athetosis, congenital cerebellar syndromes, and some diplegias may also present with marked hypotonia and apparent weakness in the early stages. The finding of fasciculation in the tongue and limb muscles is of great diagnostic significance. Essentially the differential diagnosis is from other diseases of the motor unit (Table IV). The progressive and

TABLE IV

Differential diagnosis of diseases of infancy which can affect the motor unit

Motor neurone	Acute spinal muscular atrophy (acute Werdnig-Hoffmann disease) Chronic form(s) of spinal muscular atrophy Congenital neuronal dysgenesis (causing some forms of arthrogryposis) Infantile acute poliomyelitis
Peripheral nerve	Diphtheria Guillain-Barré syndrome Pink disease Hereditary neuropathies, e.g. Charcot-Marie-Tooth
Neuromuscular junction	Myasthenia gravis
Voluntary muscle	Congenital muscular dystrophy Mitochondrial myopathy Nemaline myopathy Myotubular myopathy Central-core disease Muscle glycogenosis Dystrophia myotonica Myositis

generalized nature of the disease will in time exclude poliomyelitis and neuronal dysgenesis. Nerve conduction studies (Gamstorp, 1963) and the demonstration of normal CSF components make a peripheral neuropathy and the Guillain-Barré syndrome unlikely. The history and an edrophonium (Tensilon) test will exclude both forms of infantile myasthenia. Electromyography may (and usually does) give positive evidence of motor neurone involvement, and in some cases will exclude a myopathy, though in the early stages of this latter group of diseases this is not always reliable.

Muscle biopsy (ideally with histochemistry in addition to standard microscopy) will confirm a

neurogenic picture on the one hand, or may show myopathy if such is present on the other. However, in the presence of positive electrodiagnostic findings and a normal CSF, muscle biopsy (as opposed to necropsy confirmation) is usually unnecessary especially where the typical clinical picture with fasciculation of either tongue or small limb muscles is present.

When considering possible alternative diagnoses, a potentially treatable infantile condition like peripheral neuropathy or polymyositis, or one with an essentially better prognosis like some types of congenital myopathy needs to be thought of. Moreover, if spinal muscular atrophy is established as the anatomical diagnosis, it is important to specify further which particular genetic disease is involved (Emery, 1971; Pearn *et al.*, 1973). That is, a definitive diagnosis must include genetic as well as pathological considerations as management and prognosis depend on both these factors.

Recurrent bouts of pneumonia, initially hypostatic, are the rule. Dubowitz (1964) feels that the use of antibiotics does not materially increase life expectancy in this acute infantile disease, and certainly the ages of infants in case reports of 50 years ago seem comparable with those of today (see reviews by Reuben (1917); Greenfield and Stern (1927); Brandt (1950); Byers and Banker, (1961)). All criteria of intellectual development (eye following, stimuli response, onset and quality of vocalization, and stranger response, etc.) suggest that mental development is not retarded. For this reason the infants need extra affection and care, and intelligent modification of their environment to provide stimuli which do not require manual activation.

This leads us to mention perhaps the most important feature of these infants' lives, that is, the maternal response to their illness. Many mothers are frightened of these babies, and most of them fear the future. A number of these infants with Werdnig-Hoffmann disease died suddenly without warning and without premonitory evidence of pneumonia; the association of such events with recent feeds suggests that inhalation may be a danger. Bulbar involvement is invariable in this acute disease.

For these reasons management must be centred on the family doctor. Some mothers frankly ask for guidance about what to expect in the terminal stages. The situation of a young mother alone in the house with a moribund or dead infant is naturally a fearsome prospect to many; nor is experience with a previously affected infant necessarily of any help. Occasional overtones of guilt because of

genetic implications may aggravate the situation further.

Prognosis in this group can be accurate in the great majority of cases. Sib-pair correlation coefficients for most manifestations of the disease (age of death, etc.) are high enough to allow one to use a previous sib's history as a guide to prognosis in a current case. This is not necessarily true of chronic forms of spinal muscular atrophy. One difficulty is in being certain that one is dealing with true acute Werdnig-Hoffmann disease and not a chronic form of spinal muscular atrophy, but we believe that such a distinction is possible on clinical grounds (Pearn *et al.*, 1973).

Genetically the disease is transmitted as an autosomal recessive, and, assuming that a single gene locus is involved, the approximate carrier frequency is 1 in 70 in this country. However, parental consanguinity rates are increased and were approximately 5% for families in this series compared with the national average of about 0.1% (C. O. Carter, personal communication, 1972). An increase of this order probably indicates the presence of more than one mutant gene. The relatively low incidence of 5% consanguinity in affected families is in keeping with the finding that the more common a gene for an autosomal recessive condition, the smaller is the expected increase in parental consanguinity rates for parents of index cases (C. O. Carter, personal communication, 1972; Li, 1961). Carrier detection is not possible at present as one has no clue either to the biochemical lesion underlying acute Werdnig-Hoffmann disease or to potential heterozygote manifestations.

Acute Werdnig-Hoffmann disease is one of the more difficult diseases confronting the paediatrician today. Differential diagnosis is wide but a specific diagnosis can be made in virtually all cases. Management, prognosis, and genetic counselling can be appropriate only if such a specific diagnosis is established. Subsequent care has, as its central theme, parental support set in the context of an understanding of the natural history of the disease.

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Correspondence to Dr. J. H. Pearn, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE.