Chronic generalized spinal muscular atrophy of infancy and childhood

Arrested Werdnig-Hoffmann disease

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Pearn, J. H., and Wilson, J. (1973). *Archives of Disease in Childhood*, **48**, 768. **Chronic generalized spinal muscular atrophy of infancy and childhood: arrested Werdnig-Hoffmann disease.** Recent studies have shown that the acute fatal form of infantile spinal muscular atrophy (acute Werdnig-Hoffmann disease or spinal muscular atrophy Type I) is a distinct genetic and clinical entity. This has prompted clinical re-examination of the disease known as 'arrested Werdnig-Hoffmann disease' which hitherto was thought to be a spectrum variant of the acute fatal form. A total of 18 such patients with the chronic generalized form of spinal muscular atrophy has been known to The Hospital for Sick Children over the past 10 years. Patients with this characteristic clinical syndrome comprise approximately one-fifth of children with chronic spinal muscular atrophy. Clinically, no patient was even able to crawl normally or progress further with motor milestones. Median age of clinical onset is 6 months of age, and life expectancy ranges from 2 years to the third decade. Inevitable spinal and joint deformities occur by the second decade of life. Management should be based on vigorous antibiotic therapy, orthopaedic and neurological surveillance, and a carefully planned educational programme aimed at realistic employment in late adolescence.

The spinal muscular atrophies (SMA) of childhood comprise a group of diseases about which there has been little nosological agreement. Consequently, clinical guide-lines have been blurred. Though anterior horn cell disease can affect children of all ages, it can be shown that the acute infantile form, classical Werdnig-Hoffmann disease (WHD), is not simply a spectrum variant of SMA, but rather a discrete genetic entity (Pearn, Carter, and Wilson, 1973) whose clinical boundaries can be defined (Pearn and Wilson, 1973).

A personal study of the chronic group has revealed that one-fifth of such cases manifest clinical signs indicating significant and generalized muscle involvement before the age of 2 years, and probably much earlier. Such cases apparently do not show the relative proximal or distal differentiation of weakness nor the selectivity of muscle changes characteristic of Kugelberg-Welander disease (Kugelberg and Welander, 1956), or of its infantile

variants (Fried and Emery, 1971; Emery, 1971) of neurogenic forms of the scapulo-peroneal syndrome (Kaesler, 1965), or of the rarer distal SMA (Dyck and Lambert, 1968; Meadows and Marsden, 1969). Trunk, cervical, bulbar, and perhaps facial involvement occurs relatively early (usually by 3 years of age) in this chronic generalized group.

In so far as these features constitute a striking clinical syndrome that occurs in patients (and in the majority of, but not all affected families) who are quite distinct as a group from those with the acute form of SMA (classical WHD), we review our experience with them. The group has been recognized clinically for many years and has usually been termed 'arrested Werdnig-Hoffmann disease' in this country, or as 'the Dubowitz variant of Werdnig-Hoffmann disease' (S. Bundey, personal communication, 1972) in the United States.

Several excellent combined clinical and laboratory studies (e.g. Dubowitz, 1964; Gardner-Medwin, Hudgson, and Walton, 1967; Gamstorp, 1967; Munsat *et al.*, 1969) have reported experience with

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this group, but in the light of our own large survey of SMA we now feel that such reports included cases of SMA which manifested significant muscle selectivity from the beginning. The former special clinical group with severe generalized manifestations is of particular interest as it is in this group that (a) confusion exists in its differentiation from classical WHD, which is also generalized, and (b) special problems of management are encountered. We are uncertain whether the chronic generalized group is a distinct genetic entity, but our more recent evidence suggests it is not; however, sib concordance for its clinical features is high.

This paper reports the clinical findings of all patients with chronic generalized spinal muscular atrophy who have been managed at The Hospital for Sick Children over the past decade.

Methods

Series. The 18 cases of chronic generalized SMA described here are from a complete series (166 patients) of all cases of SMA presenting to this hospital between 1961 and 1970. Histological, electromyographical, and clinical criteria of the diagnosis of SMA are described elsewhere (Pearn *et al.*, 1973), as are details of motor development and their interpretation.

Selection. Using criteria previously described (Pearn and Wilson, 1973), we have classified 78 patients as suffering from classical acute Werdnig-Hoffmann disease (see Table I). In our experience a child living beyond the third birthday does not have the acute

FIG. 1.—Frequency distribution curves for all forms of generalized spinal atrophy. Age at death. The shape of the curve for the acute disease (Werdnig-Hoffmann) is known with accuracy, but the shape of the curve for the chronic disease is an estimate. The range of the modal age-at-death is probably 8 to 15 years of age. The upper limit of life expectancy is not known.

differed by more than one point on the MRC Clinical Strength Scale (Medical Research Council, 1943). In patients who died we have relied on documented medical examinations during early life showing generalized involvement without proximal/distal selectivity from the beginning, and on parents' descriptions of their children. Using these criteria, 18 patients manifested this syndrome.

Examination. 13 of the 18 patients (9 males and 9 females) were alive at the time of the study. 12 of these were re-examined (J.P.) and 12 received neurological supervision (J.W.). Each of the 15 mothers was interviewed in connexion with this specific research study and details of milestones, clinical onset and progression, and the genetic kindred were documented.

Results

Relative frequency of chronic generalized cases to other chronic patients. Table I shows the relative proportions of cases within this unselected series of all chronic patients. Very little relative selection *within the chronic groups* will have occurred over the decade sampled. It can be stated confidently that the figure of 20% (18 out of 88) is an acceptable working estimate of the relative frequency of this clinical form within the chronic childhood group.

Relative frequency of acute to chronic generalized cases. Before the objective demonstration of the clinical and genetic identity of the acute fatal disease (WHD) the appropriate question here was 'What percentage of the acute generalized cases become arrested in their downhill progression?' Unfortunately for analysis, significant selection of acute cases occurs before referral to any big centre. Virtually all chronic generalized cases eventually become known to institutions offering specialist diagnostic, paediatric, or neurological facilities,

TABLE I

Relative proportion of chronic generalized SMA to other chronic spinal muscular atrophies in a large (166) unselected series of cases of SMA occurring in childhood

Spinal muscular atrophies	No. of cases
All cases of SMA	166
Cases of acute fatal Werdnig-Hoffmann disease	78
Chronic SMA with relatively severe proximal involvement (Kugelberg-Welander variants)	70
Chronic generalized SMA	18

disease, though the converse is not necessarily true because of the overlap between these diseases (see Fig. 1). For this reason a child with SMA was defined as suffering from the chronic generalized form if (i) he survived beyond the third birthday or had a sib who did (the justification of this proviso can be seen by reference to Fig. 1), (ii) his pattern of muscle involvement was such that no selective proximal/distal differentiation was present. We have done this for living patients by excluding cases whose quadriceps/gastrocnemii and biceps/extensors carporum strength ratios

whereas a smaller and *unknown* percentage of all acute SMA becomes known. Such information must await the analysis of a total population study and this is now in progress. Though the birth ratio of chronic to acute generalized forms of the disease is still unknown, it probably is not greater than 18 in 78; that is, it must be a maximum of 23% and is probably in the range of 10 to 20%.

Developmental milestones. In using the above criteria of selection the group presents a strikingly constant picture of motor development (see Table II). Less than 25% were ever able to sit unsupported in a qualitatively normal way. None was ever able to crawl normally, shuffle, pull-to-stand, or walk. Nevertheless, the median age of clinical onset is still later by at least 3 months when compared with that of the acute WHD group. This finding agrees with that of Byers and Banker (1961), who also found that age of onset was significantly related to life expectancy.

TABLE II

Developmental motor milestones of 18 children with chronic generalized SMA

Developmental milestone	No. of children achieving skill
Ability to kick legs	12
Lifts head from prone position	11
Ability to roll over	5
Sits unsupported	4
Crawls, rolls over, pulls to stand, walks	0

Age at clinical onset of the disease. Using motor milestone data of the all-or-none kind (e.g. 'never was able to roll over') combined with 90th to 97th centiles for normal children (Frankenburg and Dodds, 1967; Bayley, 1969; Zdanska-Brincken and Wolanski, 1969), we have been able to specify retrospectively the latest stage by which the disease was producing clinical effects. These results are shown in Fig. 2a. Specification of such an infant's age does not mean that signs are not present earlier, and in this sense this technique yields a crude estimate. However, it is the most objective method known to us; errors inherent in it must be towards a false later onset and must be exclusively type I in nature statistically, and not a mixture of type I and type II errors. Even so, our results tend to show an earlier onset than assessment of clinical onset by other workers. This later age of onset recorded in the past may be due to the fact that parents have a tendency unwittingly to underestimate the age at

FIG. 2.—(a) Age when clinical signs are manifest. 18 children with chronic generalized SMA. Ages shown are calculated from motor milestone data and represent the latest possible age when the first signs are definitely present. (b) Comparison between ages of onset for acute (Werdnig-Hoffmann) and chronic forms of generalized SMA. Only after a child is known to have been clinically normal at 6 months is the diagnostic differentiation absolute between the two groups.

which motor milestones are passed (Donoghue and Shakespeare, 1967; Neligan and Prudham, 1969). If this is so, then retrospectively the child will appear to have been unaffected until relatively late.

In the present series the ranges of the latest possible clinical onset of the disease was 3 to 12 months, with a median of 6 months. This overlap with the acute forms (see Fig. 2b) poses diagnostic difficulties, but there are clinical guide-lines to separate them (Pearn and Wilson, 1973). None of the mothers reported sensation of abnormal fetal movements, contrasting with a minimum of 30% of mothers who experience this phenomenon while bearing a fetus with the acute fatal infantile form of WHD (Pearn, 1973a), which is genetically distinct. We have recorded the child's age when first taken to a doctor because of parental concern about weakness or failure to progress in motor development. Parents differ in their tendency to consult a doctor early, but we found this 'milestone' (often verifiable) helpful as an indicator of general

chronicity trends (Pearn *et al.*, 1973), the range being 6 to 22 months with a median of 10 months. A comparison with children having the acute generalized form is shown in Fig. 3, where it can be seen that in the past this feature has acted as a good discriminant, and is possibly helpful in counsel and prognosis. This may not, however, always be true, especially in situations where there is close neuro-developmental surveillance of infants.

Life expectancy. This is very variable and because of the gross deformities of these children (see Fig. 4) and of the universal paresis, they are at constant risk. The youngest died at 2 years of age and the oldest is still alive at 22 years but has been artificially respired every night for the last 5 years. Because 9 of the children were still alive at the time of the study, it is not possible to give accurate survival figures. However, 13 (72%) were still alive by their fifth birthday and 6 (33%) were alive

disease (see Fig. 1), and in the parents subjectively interpreting the implication of the 1 in 4 risk involved (C. O. Carter, personal communication, 1972; Pearn, 1973b). There was no consanguinity among parents, a finding in keeping with that of Dubowitz (1964) and Munsat *et al.* (1969). This is indirect evidence that the carrier rate of the recessive gene involved is relatively high, possibly in the range of 1 in 100 to 1 in 150.

Clinical progression. Initial clinical progression was relatively slow, but within 1 year from the time of clinical onset all patients manifested gross generalized hypotonia and paresis (Fig. 4). Though the muscles of all limbs were severely affected, there was invariably some asymmetry of subjective muscle strength and usually some asymmetry in clinical signs, a phenomenon also reported by Dubowitz (1964). Scapular muscles were less severely involved than other upper limb-girdle muscles. Triceps were usually less severely affected than biceps, hamstrings less than quadriceps, and thigh adductors less than abductors.

Viewed against a time-base measured in years, all older patients felt that continued deterioration had occurred, but often in a step-wise manner. Step-wise deterioration may be associated with inter-current infection (see also Case 20 of Munsat *et al.*, 1969). In most cases progression was so gradual that for practical purposes arrest could be considered to have occurred. We agree with Munsat *et al.* (1969) that a common course was one of slow deterioration and then intermittent stabilization. No child had deep tendon reflexes after 2 years of age, and the loss of these may well have occurred earlier.

All children developed some degree of scoliosis by 3 years. Joint contractures were virtually universal in later childhood, and gross orthopaedic abnormalities (Fig. 4) were common by the middle of the second decade. Gross chest deformities made management of the inevitable recurrent pneumonic episodes difficult. Because of 7th nerve involvement (and probably the motor component of the 5th cranial nerve also) facial muscle imbalance resulted in characteristic changes in facial appearance. Respiration became solely diaphragmatic (which remains strong), but required assistance in the one case in this series surviving into the third decade. Intellect was within normal range and the children were generally happy.

Discussion

The cases of chronic generalized SMA (arrested WHD) described here constitute a homogeneous

FIG. 3.—Range of ages at which affected children are first taken to the doctor, giving an indication of general chronicity trends. In the past the acute and chronic forms of generalized SMA have been differentiated by this criterion. The apparent discontinuity without overlap may be bridged with progressively improving neuro-surveillance of infants.

by their tenth birthday. We provisionally regard the modal age at death to be in the 8- to 15-year range at this stage of knowledge. The youngest boy died at 2 years of age and his sister is alive aged 17. The youngest girl to die was almost 5 years. Dubowitz (1964) has noted that males seemed to be more affected by the disease than females, and this is our impression also.

Genetics. 15 families were involved, 3 having 2 children affected. No member of a previous or subsequent generation was affected. These findings agree with the accepted concept that these conditions are usually due to autosomal recessive genes. 1 family was particularly interesting as 1 sib (a boy) died at the age of 2 years, whereas the index sib (girl) is alive, albeit grossly disabled, at 17 years. Such a family is of great theoretical value, helping to define the clinical range of the

FIG. 4.—(a) 12-year-old boy with chronic generalized SMA. Note the gross thoracolumbar lordosis and the fixed flexion deformities of the hips, knees, and feet. Both proximal and distal limb muscles are equally involved. (b) 7-year-old boy with chronic generalized SMA. Loss of muscle bulk of both proximal and distal muscles can be seen. (c) 21-year-old woman with chronic generalized SMA. Legs are completely paralysed. Fixed flexion deformities of hips, knees, ankles, and toes are present. Clinically, virtual complete atrophy of quadriceps, peroneal, and calf muscles has occurred. (d) 3½-year-old girl. Upper and lower limbs and limb-girdle muscles are extremely weak. Universal hypotonia. Lordosis and scoliosis are already present.

group clinically, and because of the characteristics of this syndrome these cases are considered as a group in this report. Such cases have been known and reported for many years (Werdnig, 1891; Brandt, 1950; Walton, 1957; Zellweger *et al.*, 1969). Many workers have commented on the generalized nature of the muscular involvement (Dubowitz, 1964; Cases 22, 23, 24, and 28 of Zellweger *et al.*, 1969). The combination of such profound paresis and a normal intellect is unusual in paediatric practice. Specific conditions of severe weakness such as Duchenne muscular dystrophy are often associated with some intellectual impairment (Cohen, Molnar, and Taft, 1968) and almost half (44%) of all motor handicapped children in general

have some degree of mental retardation (Lagergren, 1970). The normal intellect of this group of patients (Dubowitz, 1964) makes their management most rewarding. Indeed, in our experience these

patients have been an influence for good in their microenvironment, and one is not confronted with any philosophical or ethical dilemma about vigorous therapy when the need arises.

Management, which should be carried out by a collaborating team, consists of vigorous treatment of intercurrent infection, physiotherapy, orthopaedic help in the management of trunk and limb deformities, and genetic advice.

The most important facet of management of these children is undoubtedly help in guidance of the parental attitude to them. In our experience the patients' longevity, health, happiness, and potential depends on parental handling of the long-term situation, perhaps more so than in other paediatric diseases. The dynamics of parental acceptance of, and interaction with, handicapped children in general are well understood (Pinkerton, 1970). In the case of this extreme form of physical handicap with its complete dependence, parental overprotection is the commonest form of deviant relationship, and one which naturally intensifies with the years.

The prevention of orthopaedic deformities is of great importance. Unfortunately, by the time children are old enough for formal active exercise, weakness is extreme and exercise usually physically impossible. Swimming and hydrotherapy, which are of great value for the more benign forms of SMA (J. N. Walton, personal communication, 1973), are not practical for the older affected child with gross flaccid paralysis, as the fear of even momentary submersion is very great. We stress that this is entirely different from the situation in other severe forms of SMA and some other neurological conditions where swimming is of great value. However, passive exercises conducted by parents on a routine basis are very important. Postural drainage is crucial, and all the older patients have found great relief from it. Acceptance of orthopaedic appliances has been low in this group, and almost all the parents and the children in the 5- to 12-year age group have rejected these. However, spinal jackets are required for comfortable respiration in the two eldest surviving patients and they become distressed without them. We strongly encourage the use of such jackets in younger patients in an attempt to minimize the deforming effects of the disease.

Sophisticated electronic equipment for the handicapped is of particular value. Pressureless switches and mouth-activated patient-operated aids (e.g. System 7 or Possum)* and specially

modified household equipment give children and adolescents the independence which is so essential for their personal dignity. We have found the ingenuity of parents very heartening in this regard.

Dietary control is essential if obesity is developing, as management of these children is greatly facilitated if they do not become obese, though one does not often see in practice the disappointing results of attempted weight control so much a feature of Duchenne dystrophy.

Education should emphasize subjects like linguistics, authorship, and mathematics, which offer a real prospect of wage-earning employment, under home conditions if need be, if the child survives to adolescence. For this reason schooling should be pushed to the tolerable limit, and extra provision made early for television, music, and a good encyclopaedia in the home. Electronic page-turners may be necessary. Pets are of great benefit, especially a dog, which in some cases in this series was trained to be a second pair of hands as well as a constant companion.

The genetic implications of this disease are very important. A subsequent affected sib is likely to follow a course defined only by the limits shown in Fig. 1. For example, if a family has lost a child at $3\frac{1}{2}$ years of age from this condition, a subsequent affected child may survive into the third decade, and parents should be made aware of this eventuality when further children are being considered. The situation is quite different from that of acute Werdnig-Hoffmann disease where the life expectancy of a second or subsequently affected sib will approximate to that of an earlier affected child (Byers and Banker, 1961; Pearn *et al.*, 1973).

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