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Hypsarrhythmia and infantile spasms

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HYPSARRHYTHMIA AND INFANTILE SPASMS

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INTRODUCTION

Almost 126 years ago, there was published in the Lancet a letter describing a peculiar affliction consisting of infantile seizures and mental retardation. The author of that letter was one W. J. West, and the case so clearly described was that of his own infant child. In the letter West, both as scientist and troubled parent, appealed for what--ever help was available, but although others at that time were aware of the condition, there was no known treatment to reverse or arrest the child's worsening condition.

Since that time a great deal has been discovered and published about the 'syndrome' of infantile seizures and mental retardation first clearly described by West in 1841. The bulk of the literature, however, dates from the advent and utilization of electroencephalography. Using this new technique, the syndrome has been elevated to a triad with the discovery of a usually associated and specific electroencephalographic abnormality usually referred to as 'hypsarrhythmia'.

In spite of the efforts of researchers in this country and abroad, the full story of 'Infantile Spasms', as it is now generally referred to, has not yet been fully elucidated, and full knowledge as to causation and effective therapy has yet to be discovered.

It is the purpose of this paper to review the historic and recent work concerning the problem of Infantile Spasms.

REVIEW OF THE LITERATURE

One of the problems associated with reviewing a subject in many publications spanning more than a century of medical progress is that of terminology. This study was no exception, in that through the years many different names for the affliction and for the seizures have been used, and to such a degree that a short review of nomenclature is both necessary and informative.

As stated above, West was the first person to publish a description of this form of epilepsy. As he described the seizure there were two main characteristics; the sudden jerk of the trunk and arms, and repetition of the same to form a regular series. He was describing his own child, who in retrospect seems to have been typical in manifesting as trunk flexion, and for these seizures he coined the term 'salaam spasms'. Other authors have coined terms to describe the same type of seizure pattern, like 'Grusskrampf' by Asal and Moro in 1924 and 'jack-knife convulsion' by Kellaway in 1952, but other workers have considered these terms misleading as they do not include or describe the other seizure patterns which may be present. As described by Willshire in 1851 and labeled as 'Nickkrampf', the spasm may be only slight and involve only the neck and shoulders. The speed and transiency were emphasized by Asal in 1924 when he used the term 'Blitzkrampf, and at the same time he recommended an all-inclusive term 'Blitz-Nick-Salaamkrampf' or 'B.N.S.'. French literature on the subject is repleat with the term invented by Gestaut and others in 1959, 'encephalopathie myoclonique infantile avec hypsarhythmie', usually abbreviated as 'E.M.I.H.'. Many other terms such

as 'propulsive petit-mal' coined by Janz in 1915 are far too nonspecific. At present the most popular and widely used term is that coined by Gibbs and Gibbs in 1952: 'Infantile Spasms'. Some authors, however, have also criticized the use of this term because of the other neurological meaning of the word 'spasm'. But as no better term is as yet available, the malady is best referred to as 'Infantile Spasms', and that term will be used in this paper.

Since the advent of electroencephalography it has become possible to more clearly evaluate the earlier literature, and it becomes apparent that in several instances a number of non-epileptic cases have been included in case series. That factitious cases were being included was noticed even before recent times when Fere mentioned this in his studies of 'Tic de Salaam' in 1883. But since the delineation of this syndrome into its triad of spasms, retardation , and a characteristic abnormal brain wave; the 'static seizures' described by Hunt in 1922 and the 'head nods' of Hadden in 1890 as well as others seem out of place by our current standards.

Recent work dates from the first account of the triad given by Vazquez and Turner in 1951, when they described ten cases of the 'new' syndrome. Using 1951 as the turning point in the research into the nature of Infantile Spasms, one can consider the work done before that time quite differently than the work done since that time, and accordingly, the older work will be reviewed in less detail then the recent work

Literature Prior to 1951

As mentioned above the original description of what we now know as Infantile Spasms was written by W. J. West in the Lancet in 1841. Following his initial communication, there is relatively little in the British literature of significance until 1955. Newnham, however, described four cases of 'eclampsia nutans' in 1349 and Barnes likewise described one case of the same disorder in 1873. Illingsworth broke a long pause in British interest in the problem with his concise description of twelve cases in 1955. Although his work is of relatively recent date, it is to be classed with the 'older' works because of its lack of electroencephalographic correlation.

On the continent however, there were many more reports published on the subject in the years following West's original report. In 1883 Fere ably reviewed the subject and reported some of his own findings. His paper included a list of synonyms used to describe the seizures. He at that time coined the term 'tic de salaam' and relegated other terminology to useless--ness as being too confusing. He also noted variations in the types of seizures presented, and reported head nods and some unilateral cases. He was the first to note a variable prognosis, in that the seizures may or may not disappear, and was the first to classify the cases etiologically into symptomatic and idiopathic groups.

Asal and Moro first used the still popular German term of 'Blitz-Nick Salaamkrampf' in 1924. In addition to describing the spasm, retardation, and the occurrence of spasms in series, they also mentioned the cry which is often associated with the spasm. In 1926 Lederer reported on a dozen cases and in his discussion noted the normal development of the infant up

to the onset of the seizures, at about four to six months of age. He also noted microcephaly in several of his cases, and in conclusion recommended the term 'pallidum epilepsie' based on his theory that the problem had an organic basis centered in the pallidum.

One of the most important works prior to 1951 was that of Zellweger in 1948 in which he described some 94 cases . The English translation of the original German was the first reference to the classification of the cases into symptomatic and idiopathic groups . Some of his statements are disagreed with by later workers. He felt that there was no relation to perinatal insult or injury and that development is normal until onset of seizures. He was, however, the first to seriously investigate the problem of mental retardation associated with this problem. He noted that the majority of his cases were mentally subnormal and except in a few cases remained so. He was also the first author to note a possible sex factor in that his case ratio was 57:37, males to females.

In 1950 Lennox and Davis described a series of children with massive myoclonic jerks which he described as infantile spasms, and for the first time there is a mention of an associated brain wave pattern in that what he described as 'slow spike and wave' patterns were seen in over half the cases, but then no special mention was made as to there being any particular or abnormal pattern of interest in the E.E.G.

Thus by 1950 the clinical manefestations had been well established and described. The almost invariable association of mental retardation with the spasms was noted. The major and minor types of spasms had been reported, and their repetition into a series was also noted. Some authors had noted evidence of cerebral damage, but no progress on etiology or treatment was made, and no charcteristic E.E.G. pattern had been definitely associated with the spasms.

Literature After 1951

As has been mentioned above, in 1951, Vazquez and Turner described ten cases of a new syndrome - 'epilepsia generalisada en flexion,' composed of flexion spasms, mental retardation, and an abnormal electroencephalogram, which showed diffuse disorganization with paroxysmal dysrhythmia with petit mal-like spike and wave elements. They noted that such a pattern was quite dissimilar to the classical three per second spike and wave associated with other well known forms of epilepsy. Among the cases they reported, the abnormal brain wave was noted in 90% of the cases, and in all the cases the spasms started in the first year of life. An added feature of their report was the fact that they performed pneumoencephalograms on 70% of their cases and found abnormality in all those so studied. In light of the completeness of their study, their paper was indeed the first to describe the complete syndrome, on the basis of clinical, developmental, electrical and radiological findings.

In the next few years several studies were published concerning the problem of infantile spasms and its association with characteristic brain wave abnormalities. Gibbs and Gibbs published the first of several works in 1952 when they described 132 cases of their own, and in like manner published work began to appear in quantity throughout the world.

Thus we may indeed regard 1951 as the start of a new era in the history of the syndrome, and the literature review from 1951 onwards will concern itself with the clinical and electrical manefestations as well as the treatment and prognosis.

Clinical Manefestations

The cardinal feature of this syndrome is the spasm. In general, the characteristic spasm is described as being sudden, brief, and generalized. In appearance it is not unlike a massive myoclonic jerk. The duration may vary- from being extremely rapid (Blitzkrampf) to lasting longer than the above mentioned adult type myoclonic jerk. The commonest form is the truncal flexion spasm in which the arms are outward and forward, and the legs similarly flex at the hips- the salaam spasm. As was noted by earlier authors two other types of spasms are seen, even though less commonly, and these manifest as hip extension and nodding of the head or 'Nick-krampf'. In an occasional case certain lateralizing features are noted such as greater amplitude of movement on one side, or twisting to one side. Any of the spasm types may repeat to form a series which terminates by decreasing frequency and intensity of the spasms. And as was mentioned above there may be an associated cry which occurs during or after the seizure.

Asal and Moro were the first writers to delineate the three types of possible siezures in 1924, and their statement that the flexor type or salaam spasm is the most common and lasts the longest holds today. Zellweger in 1948 felt that the nodding spasm was only a minor flexion spasm, and this was agreed with by Livingston in 1958 who added that they may present in series, like flexion spasms.

Spasms presenting as extension are considered to be relatively rare. In 1950 Lennox noted this in his case series report and this was backed up by Bernard in 1958 who found no extensor spasms in his twenty cases.

Of the forty cases described by Druckman in 1955, fifteen presented with extensor spasms. In the same paper, however, they reported that flexor and extensor spasms could exist together and that flexor spasms could occasionally change in presentation to mixed or extensor spasms. In 1958 Thieffry reported a series of thirty six cases and described only two of the extensor type. Of all the authors reviewed, none were found who would disagree with the assumption that flexor, extensor, lightning and nodding spasms belong to the same syndrome and are nothing but clinical variants, all to be considered infantile spasms.

Due to the fact that an infant who can walk or stand will usually fall when experiencing a salaam spasm, certain authors have included akinetic attacks as a possible manifestation of this syndrome (Livingston et al. 1958). Bower and Jeavons disputed this idea by simple observation of muscle tone during spasms suffered by their patients, as well as pointing out that the classical E.E.G. pattern of akinetic attacks, the three cycles per second spike and wave described by Lennox in 1945, was absent in all their cases.

That the spasm is of brief duration is agreed to by all authors. In 1924 Asal and Moro reported an average time of two seconds. Thieffrey reported one to thirty seconds in 1958, and Roger agreed with one second or longer in his 1960 case series report. In none of these papers were there distinctions made as to type of seizure, thus the combination of 'lightning' and 'salaam'attacks probably accounts for the variation in times.

Electromyography during spasm has been studied by both Pampligione and Roger in 1960, and a pattern consistent with tonic spasms and 'grand mal' was noted in each of the several cases studied. Pampligione denied any spinal origin for such spasms in his report.

Few authors give mention to any lateralizing or focal elements in the spasms of their case series. Jeavons and Bower, however, noted such features in thirteen percent of their 112 cases in 1964. They also noted that almost all of these cases were of the symptomatic group.

Druckman and Chao reported that it was common to find that the 'twilight state', just before sleep or upon waking, acts as a precipitant to spasms. In the same 1955 paper the authors reported that feeding also acts as a stimulant but that sudden noise or other sensory stimuli are seldom noted to precipitate attacks. Deschamps pointed out in 1958 that a normal Moro reflex in infants must be ruled out as it can also be evoked by the above mentioned stimuli. He also noted that in the Moro reflex the fingers grasp, whereas in the usual infantile spasm they are extended.

Several authors have reported the coexistance of other types of epileptic seizures in some cases. In 1952 Gibbs and Gibbs reported that nine per cent of their cases had other fits. Matthes found fifty four percent in his 104 cases and Jeavons and Bower noted other types of epilepsy at some time in fifty percent of their cases.

The second cardinal feature of this syndrome is the fact that mental retardation is found in association with the spasms. The first report of an association with data was by Gibbs and Gibbs in 1952, at which time they felt that thirty percent of their patients were retarded. In the past several years most authors report figures of ninety percent or more, such as 97% by Jeavons and Bower in 1964 , and 90% by Matthes in 1963.

Most cases have been reported as being severely retarded but formal testing of functional ability has been carried out only since the advent of steroid therapy in 1958.

Some examples of studies which have evaluated patients as to the presence and degree of mental retardation begin with the 51 patients of Baird in 1957, 43 of whom were below 50% on the Gesell developmental quotient scale, the remainder being untestable. Dailly in 1961 reports retardation in all his patients with most being under a figure of 40% on the Gesell scale. In their 1964 study of 112 cases, Jeavons and Bower reported 97% showing retardation with 78% showing severe retardation or 35% or below on the Griffith scale.

In 1955 Druckman and Chao reported that patients without series of seizures had a better mentality, and this was confirmed by Thieffry in 1958. In both of these case series, however, there was no formal testing.

As Illingworth pointed out in 1955, the retardation seen in these patients is of a differential quality. The areas of function most affected are those of the personal-social abilities. As he pointed out, there may be such severe failure in social responsiveness that the child may be considered blind by those tending him.

The third and most recently discovered element of the triad of findings composing the syndrome of infantile spasms is that of the electro--encephalographic data.

As was related to previously, Lennox and Davis in 1950 described slow spike and wave activity in cases of massive myoclonic jerks, but made no special comment as to there being any particularly unusual E.E.G. features. Vazcuez and Turner in 1951, however, stated that the E.E.G. patterns of their cases of infantile spasms showed a characteristic and diffuse disorganization with paroxysmal dysrhythmia similar to that seen in petit mal epilepsy.

The name 'hypsarhythmia' was first applied to the characteristic E.E.G. pattern by Gibbs and Gibbs in 1952 when they published the report of their 132 cases of infantile spasms. Other workers on the continent recognized the pattern and its association but assighned differing names, such as 'Type B Myoclonus' by Gestaut and Remond, and 'diffuse gemischte kampf--potential' by Hess and Neulaus. However the name in most common use is that of 'hypsarrhythmia', and that name will be used here.

As first described by Gibbs and Gibbs in 1953 the characteristic record of hypsarrhythmia is composed of high voltage, random, slow waves and spikes in all cortical areas. Such spikes are variable in location and direction and may appear to arise from single or multiple foci. The spiking does not show the rhythmicity or organization seen in petit mal recordings, and in a word may be described as chaotic. The original findings of the Gibbs' have been noted again and again and confirmed by several authors including; Bernard in 1958, Dailly in 1961, and Trojaborg in 1966 as well as others.

In 1960 Trojaborg differentiated hypsarrhythmia from petit mal and petit mal variant by the lack of synchrony of abnormalities, and expressed the number of synchronous spikes as a percentage of the total spikes, and found a low figure in their cases of hypsarrhthmia. Thiebaut described several types of hypsarrhythmic record in1955, and indicated that there was a tendency for the E.E.G. to show transitional recordings.

The term 'modified hypsarrhythmia' has been used to describe atypical recordings by many authors. Druckman first used it in 1955 to describe records which showed more synchrony, and in the same manner has been used by: Bernard in 1958, Dailly in 1960, Matthes in 1963, and Trojaborg in 1966.

Gibbs and Gibbs as well as Hess and Neulaus both noted in 1952 that there was a tendency for focal spikes to occur as the disease progressed and the chaos diminished. They also noted that such foci were often situated in the temporal regions. Rebufat was one of the first to note that : records taken at an early age may not show hypsarrhythmia although it develops later. He also noted that some of the early records showed focal abnormalities. This finding has been confirmed by Matthes, who also noted as has Trojaborg in 1966, that with therapy and the disappearance of the chaos of hypsarrhythmia the focal abnormalities re-appear. There is now general agreement that with time the chaos disappears and there is a transition to a pattern of synchronous slow spike and wave discharges. Ultimately the record will either become normal or show focal discharges as has been confirmed by Jeavons in 1964 and Trojaborg in 1966.

As Gibbs and Gibbs first noted the sleeping state induces a certain amount of rhythmicity in the record, with periodic brief bursts of high voltage slow waves and spikes followed by low activity or silence. Many authors, including Jeavons in 1964, have described the sleep pattern and have suggested that hypsarrhythmia may in fact only become apparent in certain cases when the child is asleep, and thus should be taken in all suspected cases.

During the actual spasm, a discharge of fast waves and high voltage spikes is seen. But to this description by Gibbs in 1952, Hess added the description of two types of record, one with prominent spikes and slow waves and the other with a reduction in activity and a flattening of the tracing. Jeavons reviewed his cases in 1964 and noted the presence of all these types of records as well as some records showing no change at time of spasm. But he felt that the commonest E.E.G. pattern associated with

spasm was the initial spike with or without slow wave followed by a flattening of the trace with a slow rhythm with gradual increase in frequency and amplitude until the chaotic spikes and slow waves reappear.

In all of the case series mentioned thus far, it has been seen that hypsarrhythmia or modified hypsarrhythmia was found in 50 to 100 per cent of cases with infantile spasms. Livingston found it in 86 percent of his 698 cases, Matthes in 96 percent of his 104 cases, Hoeffer on 85 per cent of his 40 cases, and Jeavons in 66 per cent of his 112 cases. In all of the studies about 1 to 15 per cent will show normal or nonspecific recordings, and other epileptic or focal record appear in from 1 to 30 per cent. All of the above refer to presenting brain wave patterns, when the symptoms had become apparent.

The occurrence of hypsarrhythmia without infantile spasms have been reported in a few cases by Matthes in 1955, Baird in 1957, Bower in 1959, Trojaborg in 1961 and 1966, and Hoeffer in 1963. Most of those cases showed evidence of cerebral damage, were retarded and had seizures, of various types.

Jeavons and Bower in 1964 summarized the problem and stated that the E.E.G. is very useful in the confirmation of cases of infantile spasms and that a normal record makes the diagnosis unlikely. They also noted that in about one third of cases the record will be epileptic but not hypsarrythmic.

It is generally agreed by most authors that hypsarrhythmia is an E.E.G. pattern associated with infancy only, and that it disappears with age. The pattern is uncommon after the age of four or five years, as was shown by Hess and Neuhaus in 1952 when the disappearance in 94 per cent of their cases by the age of five and all by the age of seven. This finding has

been confirmed by Jeavons in 1961 and 1964 as well as Trojaborg in 1966. Most authors describe the course of maturation as being characterized by increasing organization of the abnormal discharges, but few mention a final development of typical three cycles per second spike and wave activity.

Some of the other clinical parameters of this syndrome include: onset in the first year of life, and a preponderance of male cases.

Most authors reviewed reported a peak age onset at six months with a range of from three to eighteen months. Roger reviewed the European literature in 1960 and found a range of from three to eighteen months with most cases in the first year of life. Jeavons reviewed the total reported cases in the American literature up to 1964 and found that 70 per cent showed onset within the first six months and 90 per cent within the first year of life, and in their own group of 112 cases reported a peak age onset of five months with only three cases beyond one year.

Most of the authors reviewed reported that the sex distribution of their cases demonstrated a preponderance of male cases over female cases which was as high as two to one. The high preponderance of 2:1 was reported by Zellweger in 1948, Gibbs and Gibbs in 1952, Trojaborg in 1960, Matthes in 1963, Jeavons in 1964, and Hoeffer in 1963. Livingston found a male to female ratio of 1.1:1 in 1958, and Volzke a ratio of 1.4 to 1 in 1967. Other authors, however, have found no difference in sex distribution, such as Thieffry in 1958 and Dailly in 1961.

Etiology and Classification

One of the original workers in this problem of infantile spasms, Fere in 1883, divided the cases into two groups, symptomatic and idiopathic. Zellweger repeated this grouping in 1948 and it is used universally today.

In the symptomatic group there is usually evidence of a recognized pathologic process and it is usually found that mental development was retarded before the onset of infantile spasms. In the idiopathic group the child is usually noted to have developed normally and to have been o of normal health until the sudden onset of spasms, and to be retarded developmental-wise after the onset of spasms.

Many authors, including Gestsaut, Illingworth, Chao, Thieffry, and Jeavons have reported that the onset of spasms was associated with the cessation or regression of mental development. Baird felt that 27 out of his 51 cases in 1957 were retarded from birth, as did Thieffry in 10 out of his 30 cases in 1958. In 1964 Jeavons felt that the symptomatic cases were retarded from birth, but pointed out the difficulty of assessing the development of young infants, especially if they have spasms at early age.

In the symptomatic group the commonest etiological factor is cerebral birth injury. Livingston found this in 64 per cent of his symptomatic cases in 1958. Gestaut in 1953, Gibbs in 1954, Druckman in 1955, Kellaway in 1959, Bower in 1961, Matthes in 1963, Jeavons in 1964, and Stephan in 1967, all commented on the etiology of symptomatic cases. These authors found perinatal and prenatal causes in from 25 to 55 per cent of the symptomatics, developmental abnormalities as causes in from 5 to 20 per cent, central nervous system infections in up to 18 per cent, and other trauma in up to 7 per cent. Jeavons points out the difficulty in deciding whether the clinical picture of brain damage is of pre- or perinatal origin in the neonatal period, and discourages a separate prenatal etiology catehory as do several other authors.

Other disorders which have been reported as being causative factors in patients with infantile spasms have been: vascular disorders, dehydration, subdural hematomata, syphilis, tuberose sclerosis, Sturge Weber syndrome, Tay-Sachs, toxoplasmosis, phenylketonuria, and disturbanced of glycine metabolism.

Immunisation against diphtheria and pertussis has been regarded as a etiological factor since the first mention by Baird in 1957. He found that 9 of his 24 cases who had developed normally up to time of spasms onset had DPT immunisation just prior to the onset of spasms. Bowere. Bowere was impressed with the frequency of cases in which the spasms started within a few days after an immunising procedure in his 1960 paper. Jeavons noted sixteen out of his 112 cases had onset of spasms within one week of an immunisation procedure. In that study 86 out of 112 were classified as symptomatic, and 39 had been immunised prior to onset. The problem of immunisations was dismissed as coincidental by Illingworth in 1957 and Livingston in 1958, but more recent work raises serious questions as to the exact relationship.

The Idiopathic group includes those cases of infantile spasms for which no apparent cause can be found. The portion of the total cases which fall into this category is usually a little less than half. Studies by the same authors mentioned in the symptomatic group above report per cent of total cases values ranging from 36 to 57, with a mean of about 44 per cent. In these cases there is normal birth and development until the onset of spasms.

In many cases of infantile spasms, especially those classed in the sympto--matic group, accompanying neurological abnormalities are found. As early as 1926, Lederer commented on the common occurence of microcephaly, and this finding is borne out by most authors, particularly in the sympto--matic cases. Cerebral Palsy is another finding frequent in the same group. Gibbs and Gibbs found it in 17 per cent of their cases, Trojaborg in 43 per cent in 1960, Millichap reported 58 per cent in 1962, and in 1964 Jeavons reported 25 cases out of 39 in the perinatal symptomatic group. An associated severe neurological abnormality, either spasticity, hemiparesis, or athetosis, was found in 51 of 73 cases by Druckman in 1955, and at the same time he found only 14 per cent free of neuro--logical abnormality. Kellaway in 1959 noted 60 per cent of 250 cases showed one of the above mentioned abnormalities, and that only 11 per cent were neurologically normal. In 1961 Dumermuth reported spasticity in 38 per cent of his cases.

Blindness in these patients has been reported and discussed by many authors since it's first mention by Janz in 1955. That interpretation and others by Thiebaut and Baird were thought to be incorrect by Illingworth in 1955. Thieffry showed in 1958 that only 2 out of 11 cases thought to be blind by investigators were actually blind. He stated that it was the severe mental retardation in those cases and lack of response to the environmental stimuli which lead the observer to the conclusion that the child could not see. At the same time Thiebaut reported true blindness and optic atrophy in 4 of 25 cases examined by him. Millichap felt that 30 per cent of their cases were either blind or manifest visual innattention in his 1962 study.

In many case studies radiographic studies are done to examine the structure of the central nervous system. Such studies usually take the form of pneumoencephalograms, and they frequently demonstrate abnormal findings. The most commonly reported abnormalities are atrophy of the cortex and dilated ventricles. The notable study by Vazquez in 1951 reported abnormality in all cases, and the same 100 per cent rate has been found by Chao in 1955, and Trojaborg in 1960. Other studies have found abnormalities of this exam in most but not all of their cases, such as Livingston in 1958 with 93 per cent, Dumermuth in 1961 with 96 per cent, and Matthes in 1963 with 96 per cent. Reviewing the European authors in 1960, Roger found figures ranging from 22 to 72 per cent. Since 1960 to present, reviewing European workers with sufficient English abstracts or summaries, the reported figures are somewhat higher, in the range of 50 to 85 per cent. As Jeavons pointed out in 1964, no work done distinguishes between the symptomatic and idiopathic groups as far as the pneumoencephalograms are concerned, and no difference in the groups has been reported.

Many workers have sought for biochemical abnormalities in cases of infantile spasms, but as yet no definite findings have been shown in the majority of cases. There is general agreement that phenylketonuria may present with this syndrome. In 1957 Low reported infantile spasms in seven of twenty-three patients with phenylketonuria whose ages ranged from seven months to forty-seven years. Six of those with spasms showed hypsarrhythmia on their electroencephalograms. Most other reports on phenylketonuria only rarely mention infantile spasms, due possibly to less interest in seizures than the more classically associated retardation.

In the more recent literature, however, since testing for phenylketo-nuria has become more common, more case series of infantile spasms have included patients with the biochemical abnormality. Dumermuth found two in his 38 cases, Millichap one in 61, Matthes two in 104 in 1963, and Jeavons one case in 112 in his 1964 study.

Although hypoglycemia is often suspected and searched for by most workers, it is rarely found in children with infantile spasms. Millichap found one case in his 1962 series, Bower found no cases in his 1961 series as had Baird in 1957. Jeavons found one case of leucine sensitive hypoglycemia in his case series of 112 patients.

In recent years a disorder of tryptophan metabolism based on a relative or absolute deficiency of pyridoxine has been reported by several authors but the significance of such findings remain uncertain. In 1959 Cochrane reported that five infants with infantile spasms showed abnormal tryptophan loading tests. He also reported that using pyridoxine in large doses he was able to produce improvement in epilepsy, E.E.G. findings, and mental level. These findings were echoed by Jeune in 1959 also. An unconfirmed finding is that of Low in 1958, at which time he reported that a diet low in tryptophan produced clinical and electrical changes for the better in one child with infantile spasms. Bower reported a normalization of the tryptophan loading test using A.C.T.H. therapy in 1961, as well as a clinical improvement. In the same study he felt that although pyridoxine improved the chemical abnormality, it did not always improve the clinical status as A.C.T.H. did. From his study and a review of other cases, he concluded that although there was evidence of pyridoxine deficiency in some cases of infantile spasms, the cerebral abnormality

was not usually reversible on pyridoxine therapy, and that A.C.T.H. must act through some other pathway. Hellstrom and Vassella reached the same conclusions in their 1962 study, and likewise could not explain the action of A.C.T.H. and steroids on the basis of a disturbance of pyridoxine metabolism. Jeavons and Bower in 1964 reported four cases on infantile spasms with abnormal tryptophan loading tests, but on the basis of their data could elaborate no further than the above conclusions.

In an extensive study of tryptophan metabolism in children with epilepsy of various types by Hughes in 1966, it was found that there is no correlation between the etiological subgroup of infantile, or for that matter any childhood spasms, and abnormalities of tryptophan metabolism. Also the presence or absence of epilepsy itself seems unrelated, as do the E.E.G. and mental findings. They concluded that tryptophan studies could provide no aid in the diagnosis of convulsive disorders.

Neuropathological correlation has never been very extensive in case reports of infantile spasms and the number of autopsy reports is small. Of the few autopsy reports that include histological details the findings, either macroscopic or microscopic are extremely variable.

In 1959 Bamberger reported one case with abnormalities in the grey matter and microgyria, which, he felt, reflected arrested cell development. Also in 1959 Kellaway described a case of porencephaly and another case with encephalitis confined to the thalamus and upper brain stem. Poser in 1960 found edema and spongy degeneration in three cases. Harris in 1962 examined tissues from 11 idiopathic cases of infantile spasms but demonstrated no significant findings structurally or on chemical analysis. Sinton in 1962 reported a symptomatic case with degeneration in the cerebellum. Tucker in 1963 reported a case with minor changes in the white matter with increased microglia and astrocytes, but no other changes. Jeavons in 1964 reported on three cases but all had non-specific or normal findings. Thus it would appear that using present methods, pathological correlation is, in general, unfruitful.

The actual cause or pathogenesis, as is evidenced by the above cited literature, of hypsarrhythmia and infantile spasms remains to be discovered. A variety of theories have been proposed by the several workers inthis field, beginning with Lederer in 1946 who assigned fault to a disordered pallidum, a view which as recent a 1958 has found support in the writings of Spiegel. Vazquez in 1951 felt that the cause was liberation or excitation in the brain stem. Gibbs and Gibbs regard the E.E.G. pattern associated with the spasms as a desynchronization arising in the reticular formation, caused by its liberation from cortical influence. This view was in part supported by Parcis in 1959 when he

pointed out that the peak onset of spasms coincided with the time of establishment of co-ordination between cortical and subcortical structures. In 1958 Deschamps commented that the slow spike and wave seen in hypsar--rhythmia is also seen in cases of cortical atrophy or cortical lesions. But Jeavons pointed out in 1964 that hypsarrhythmia has features in common with the E.E.G. seen in grand mal, and he felt that the mechanism could be liberation of subcortical mechanisms due to cortical damage, or inco-ordinated excitation of damaged subcortical structures. Kreindler in 1965 in his review of experimantal epilepsy felt that the ultimate pathophysiological mechanism was still unknown.

Treatment and Prognosis

Only in the last ten years has the treatment of infantile spasms begun to show a certain measure of success. In the past it has been virtually a hopeless undertaking. Practically every anticonvulsant known has been utilized in an attempt to control the seizures, and none have succeeded. In rare instances the barbituates have been able to at least temporarily control the spasms. Various authors have claimed success with various drugs but no consistently successful agent has been found. In some cases spontaneous remission may complicate evaluation of results.

Gibbs and Gibbs in 1954 reported that in their hands chlortetracycline was a useful agent. Their work dated from the assertion by Stamps in 1951 that chlortetracycline was a valuable agent in epileptic patients. Diet has been forwarded by several authors as a means to control, such as Livingston in 1958 who claimed complete control in 91 out of 186 cases of infantile spasms using a ketogenic diet. In 1958 Low reported that in his hands various diets deficient in various amino acids showed little benefit.

The first real advance in the therapy of infantile spasms and hypsarrhythmia dates from the work of Sorel and Dusaucy-Bauloye in 1958. At that time they reported encouraging if not dramatic results using A.C.T.H. combined with chlorpromazine. They reported cessation of the spasms, improvement and occassional normalization of the E.E.G., as well as improvement in mental functioning if the treatment were started early in the course of illness.

It is often difficult to evaluate the work of past authors concerning the results of treatment because many do not classify the cases, thus making it difficult to tell whether the idiopathic or symptomatic cases are better suited to corticotropin therapy. Also the methods of treatment vary, and the degree of E.E.G. confirmation, assessment of mental state or change in ability, and the definition of improvement differ from worker to worker.

In reviewing the results of A.C.T.H. therapy for infantile spasms and hypsarrhythmia in the literature, the number of workers is impressive.

Sorel, 1958-59
Dumermuth, 1959, 61
Gestaut, 1959
Dufresne, 1959
Thygessen, 1959
Dobbs, 1960
Fukuyama, 1960
Brandt, 1960
Chen, 1960
Kiorboe, 1960
Pauli, 1960
Trojaborg, 1960, 66
Allen, 1961
Dailly, 1961
Low, 1961
Scheffer, 1961
Degen, 1963
Finne, 1963
Matthes, 1963
Petersen, 1964
Schmidt, 1964
Helstrom, 1965
Chieffi, 1965
Jeavons, 1964
Maccgnani, 1966
Alvin, 1966
Volzke, 1967

In all of the above group of authors, which is by no means the entire list but only those writing or translated in English, there is represented a total of over eight hundred cases of infantile spasms and hypsarrhythmia treated with A.C.T.H. or steroids. In compiling the average findings, which can be expected to have more validity than individual results, the effect of steroids is generally impressive. In slightly over 60 per cent the authors claimed to have brought about cessation of seizures. In 75 per cent the spasms were either stopped or reduced, and in 25 per cent no beneficial effect was noted. As might be expected, the exact same figures were obtained when the results of the same therapy were analysed using E.E.G. results. Approximately 55 per cent showed normalization of the brain wave, 75 per cent improved, and 25 per cent unchanged.

The above data includes all the cases in each series regardless of etiologic classification. Since most authors do not break down their series in this manner it is difficult to evaluate whether A.C.T.H. will benefit one or the other class of patients to a greater degree. But of the studies which did take into account the etiologic classes, the idiopathic group is seen to have success results approximately twice that of the symptomatic group. Helstrom in 1965 reported 64 versus 36 percent by grouping showing disappearance of seizures, and 41 versus 20 percent by group showing normalization of E.E.G. In 1964 Jeavons reported that 84 per cent of the idiopathic cases on A.C.T.H. or steroids ceased seizuring versus 47 percent in the symptomatic group. As regards E.E.G.s, he reported 47 versus 33 per cent normalization on therapy.

The above data relates to the results of initial therapy with cortico--tropins or steroids and in no way represents long term results, and in fact, only a few studies have been in progress long enough to offer long term results.

Corticosteroids have been used in the treatment of infantile spasms and hypsarrhythmia since Sorel's first paper in 1958, The results have been variable and they seem to function no better or worse than A.C.T.H. Dobbs gave prednisone to ten children in 1960 and obtained improvement in two. Low reported cortisone similar to A.C.T.H. in 1960. Bower felt that A.C.T.H. was slightly better than prednisone in 1961, and this was echoed by Jeavons in 1964, and Finne in 1963.

There are a small number of reports concerning the use of dexametha-zone in the literature, most of which are favorable. Mattes and his coworker Muhlburger reported that Dexamethazone gave therapeutic results which were equal to A.C.T.H. in 1963. They gave the drug at intervals

for a period of three months and then increased the drug-free interval in the subsequent three months. Using this regimine they were able to arrive at intervals of twenty drug-free days without spasms between intervals of medication for ten days. The same plan was used for both dexamethazone and A.C.T.H. and the results were the same. Similar results were reported by Dumermuth in 1959 and 1961 comparing A.C.T.H., dexamethazone and hydrocortisone, all of which he found equal in effect.

There is general agreement that A.C.T.H. and steroids have a beneficial effect on the spasms and E.E.G., but it is clear that the immediate effects of therapy are much better than the long term effects, for the relapse rate is quite high. This was mentioned by Matthes above and also by Jeavons in 1964 with his long term follow-up series.

There is also general agreement that the effects of A.C.T.H. and or steroids are not as beneficial for the problem of mentality, for only a few cases have been reported as becoming normal or more normal. Sorel, in 1960 reported that he obtained complete cure of infantile spasms and returen to normal mental functioning in nine cases out of 47. His cases were all carefully selected to have negative family histories, normal birth and development up to onset of spasms, onset between 3 and 9 months, symmetrical spasms, typical E.E.G. pattern, and no other abnormalities. Also, all of his cases were started on treatment within one month of onset. Other studies in the literature report similar results, but in general, mental improvement is still uncommon, but may occur in selected cases especially if the initial degree of subnorm
-mality is mild, or the treatment is started shortly after the onset.

In 1964 Markham reported on the treatment of seizures in infancy and childhood, and commented that children with hypsarrhythmia responded satisfactorily to treatment with nitrazepam or Mogadon. Other reports were published by Gibbs in 1965 and Weinmann in 1966. Both of these writers reported similarly satisfactory results. One of the most recent reports and one with the greatest number of cases and the longest follow-up is that by Volzke in March of 1967. In that paper he presents 24 clinically and electrically typical cases of infantile spasms, and reports control of spasms and improvement or normalization of the E.E.G. in 13 cases, and temporary remissions in 6 cases. These results compare favorably with the other authors mentioned above, suggesting that this new agent is at least deserving of further research and trial. In the opinion of Volzke, which is echoed by Peterson just recently in September of 1967, Mogadon will benefit those patients that most fully satisfy the general successful treatment criteria set down by Sorel in 1960, and will be of lesser or no value in those patients who do not satisfy the criteria.

Remissions also occur under nitrazepam and if they are to occur, usually do so in the first six weeks of treatment. Volzke detected 2 out of 13 controlled cases with recurrence , but they responded to an increase in dosage for periods of up to two years. In the cases with temporary remission, apparently no such opportunity is available, all of these cases having reverted within two weeks.

Thus it becomes apparent that infantile spasms is becoming increasingly amenable to various forms of treatment capable of providing full, even if temporary, control of spasms in more and more cases. But the effects of therapy on the mental and motor development of such cases is less than satisfactory, being possible in many cases to halt further deterioration but failing to restore normalcy in but a few cases.

Summary of the Syndrome

The syndrome of Infantile Spasms includes three cardinal features; spasms, mental subnormality, and hypsarrhythmia.

The spasms are of three main types; flexor, extensor, and nods, but flexor are by far the most common type presented. Any of the seizure-types may occur in series, and a cry often accompanies the spasm.

Approximately 90 per cent of the cases manefest mental retardation, usually of the severe type.

The electroencephalographic pattern is abnormal in almost all cases. The classic and typical pattern shows as a chaos of slow waves and spikes known as hypsarrhythmia, but as many as one third may show other patterns.

Cases can be grouped in two general etiological categories, sympto--matic and idiopathic. In the symptomatic group pre-natal and peri-natal factors are the commonest presumptive causes of the disorder, but a wide variety of known pathological conditions may give rise to the syndrome. There is a possibility that early immunization may sometimes be the cause. Neurological and other abnormalities are found in the symptomatic group, and mental retardation dates from birth or from the known etiologic condition.

In the idiopathic group are those cases who develop normally and in whom there is no clue as to causation .

The onset of the symptoms of this syndrome is usually between the ages of 3 months and one year, with a peak onset age of 6 months.

Several cases of infantile spasms with associated metabolic disorders have been reported, such as phenylketonuria and hypoglycemia. Evidence of a disorder of tryptophan metabolism secondary to pyridoxine deficiency has been reported more frequently. The role of such disorders in the syndrome remains unclear.

Autopsy examination and neuropathological correlation has, as yet, demonstrated no consistent abnormalities or patterns.

The natural history of the disorder is such that in untreated cases the spasms tend to cease around three years of age, and are very rare after the age of five. The electroencephalogram of such cases usually loses the pattern of hypsarrhythmia and demonstrates focal or generalized discharges. Some cases will graduate to normal brain wave patterns. And some cases will go on to other forms of epilepsy. Unfortunately, most untreated cases remain mentally subnormal.

The usual anticonvulsants have no effect on the disorder. Lately dramatic effects on the spasms and the E.E.G. have been attributed to treatment with steroids, A.C.T.H., and more recently, nitrazepam. Relapse on any form of treatment is still common. Improvement in mental status is still rare, but may occur in select cases in which treatment is started early and the initially mental subnormality is mild.

Prevention of this disorder will be possible when the research into the causes of infantile spasms is complete. There would seem to be no ready answer as to causation in the idiopathic group, and basic research in the areas of neurochemistry and neurophysiology is more likely to provide such information than the present and past concentration upon the clinical features of the syndrome itself.

Thus much more research is needed, probably requiring entirely new methods and concepts for its completion, for medical science has far to go before the picture of infantile spasms, or epilepsy in general is complete.

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