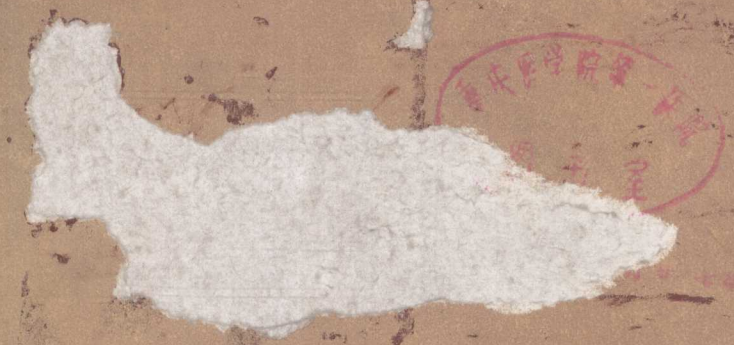
HANDBOOK OF CLINICAL NEUROLOGY

P.J. VINKEN and G.W. BRUYN

VOLUME 39

NEUROLOGICAL MANIFESTATIONS OF SYSTEMIC DISEASES

PART II



NEUROLOGICAL MANIFESTATIONS OF SYSTEMIC DISEASES

PART II

Edited by

P. J. VINKEN and G. W. BRUYN

in collaboration with

HAROLD L. KLAWANS

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Editorial Advisory Board

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Foreword to volumes 38 and 39

The current four volumes of this series, 'Diseases of Muscle' and these two volumes on the neurological manifestations of systemic disorders, bring to a close the regular volumes of the Handbook in which each disease is presented in as thorough a manner as possible. Hopefully, by now the reader is not only familiar with the organization but has some understanding of the general principles guiding the editors in making their editorial decisions.

Many of the neurological complications of systemic disorders have already been discussed thoroughly in other volumes, especially Volumes 27, 28 and 29, 'Metabolic and Deficiency Diseases of the Nervous System'. The neurological manifestations of systemic diseases were included in these volumes if the disease results in a metabolic disorder (whether or not this has been elucidated) leading to the nervous system dysfunction. Hence, the effect of uremia, liver failure and electrolyte imbalance as well as the neurologic problems due to the various endocrinopathies were all presented in these volumes.

Several other subjects which might rightfully fall within the purview of the current volumes have been covered in Volumes 7 and 8 (Diseases of Nerves) and, of course, the most common systemic disease which effects the nervous system is atherosclerosis, many aspects of which already comprise Volumes 11 and 12 (Vascular Diseases of the Nervous System).

In finally drafting these volumes, we have attempted to present those systemic disorders which directly involve the nervous system in a comprehensive manner but at the same time limiting overlap with other volumes and avoiding unnecessary repetition. Such tightrope walking can be dangerous and may result in errors of omission or commision which are more obvious to the readers than to the editors. We hope these are not too many.

Throughout the entire Handbook, a major concern of both the Editors and their collaborators is to keep the time between completion of a chapter and its publication as short as possible. The main problem has always been the failure of some contributors to complete their manuscripts within the given deadline.

Our gratitude to those authors who have managed to complete their manuscripts as scheduled is sincerely and deeply felt. We also appreciate the dedication and hard work of our desk editors in Amsterdam, especially, Mr. Robert Stanley and Ms. Deirdre Clark and also Ms. Genevieve Logan in Chicago whose overall assistance has made our work much easier.

P.J.V.
G.W.B.
H.L.K.

Acknowledgement

Several illustrations and diagrams in this volume have been obtained from other publications. Some of the original figures have been slightly modified. In all cases reference is made to the original publications in the figure caption. The full sources can be found in the reference lists at the end of each chapter. The permission for the reproduction of this material is gratefully acknowledged.

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CHAPTER 1

Leukaemia: neurological involvement

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Leukaemia can involve virtually any or all regions and functions of the nervous system. The involvement of the nervous system by the leukaemic disease process represents a serious advance in the developement of the natural history of the disease. The prognosis becomes shorter, and worse, at this juncture. As therapy has increased the length of survival in leukaemia, so has the number of cases of central and peripheral nervous system involvement increased accordingly. Ironically, the developement of nervous system leukaemia assumes paramount importance in relation to the quality and length of survival in a disease arising in a different system altogether. This is, however, merely the manifestation of the catholic nature of disease processes, and of the way in which they cut across tidy systemic anatomical boundaries, highlighting the danger of a rigid foreshortened view of the patient perceived through the confines of the various specialities.

The following account examines the various manifestations of leukaemia involving the whole or part of the nervous system. It commences with an attempt to summarise the extent, risk, chronological, and prognostic aspects, and then details various regional peculiarities, regards treatment – particularly iatrogenic problems – then infections, and finally looks at various obscure degenerative conditions.

Burns (1824) is credited with the first description of leukaemia of the central nervous system (CNS). Diamond (1934) described 14 cases and made detailed studies of the morbid gross and histological anatomy. Schwab and Weiss (1935) studied 146 cases and documented most of the now well recognised neurological aspects of leukaemia. Leidler and Russell (1945) studied 47 cases which they had selected most eclectically from the literature and added a further 20 cases of their own. More recent pathological studies have been made (Groch et al. 1960; Moore et al. 1960; Price and Johnson 1973).

The frequency of involvement of the nervous system by leukaemia has increased markedly in recent times, partly due to increased clinical awareness, and partly to the lenthening survival of cases due to the efficacy of modern treatment. The portal of entry to the CNS used by the leukaemic cells is still open to discussion. Jaffe (1934) thought that undifferentiated cells of mesenchymal origin in the walls of the cerebral veins became leukaemic in situ in response to a stimulus capable of acting on all susceptible cell systems in the body. Leidler and Russell (1945) also believed this to be a likely mechanism. Price and Johnson (1973) felt that the neuropathology in nervous system leukaemia could be divided into several stages. In the earliest stage they described leukaemic cells in the walls of the cerebral veins; later cells spread through the walls into the arachnoid, thence

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deeper, finally infiltrating the cerebral parenchyma itself.

Statistics

During the last two decades the extent to which the nervous system is involved by leukaemia has become increasingly appreciated. The increased incidence is due to the increasing longevity of patients suffering from leukaemia, resulting from the efficacy of modern treatment (Sullivan 1957; Shaw et al. 1960; Steffey 1962; Hyman et al. 1965; Nies et al. 1965; Corrie et al. 1968; Evans et al. 1970; Ravid et al. 1972; Dawson et al. 1973; Wolk et al. 1974; Bergevin 1975). Thomas et al. (1964) showed that neurological leukaemia in L1210 mice appeared only in animals whose lives had been prolonged by therapy. With increasing awareness of the propensity of leukaemic patients for neurological complication has come more investigation of asymptomatic patients and repeated discovery in such cases of active meningeal leukaemia (Pierce 1962; Evans 1963; Hyman et al. 1965; Borgstedt et al. 1970; Pochedly 1975a). Nies and coworkers, in 1965, compared observations made on two series of patients studied several years apart. This work involved children and adults. In the 1961–1963 series, the median survival of sufferers from acute lymphatic leukaemia was 4 months longer than those in the 1953–1958 series, although the survival in acute myeloid leukaemia did not increase. In the earlier study, clinically apparent meningeal leukaemia occurred in 25% of patients with acute lymphocytic leukaemia and in 4% of patients with acute myeloblastic leukaemia. In the later study the corresponding figures were 42% and 12% respectively. It was noted that if only patients in whom major neurological involvement was clinically apparent had been included, then the prevalence of meningeal leukaemia would have been approximately equal in the two groups. There were in fact, no central nervous symptoms or signs in more than one-third of 38 episodes of meningeal leukaemia which occurred in 27 patients in the later study. The greater number of patients discovered to have meningeal leukaemia was due to the performance of more diagnostic lumbar punctures.

Wolk et al. (1974) studied 299 adults with leukaemia and showed CNS leukaemia in 13% of them. The incidence was 40.5% in acute lymphocytic leukaemia, 30% in undifferentiated leukaemia, 3.5% in acute blastic crises in chronic myeloid leukaemia, and 6.5% in acute myeloblastic leukaemia. The overall incidence in this study is somewhat lower than in many others. Autopsies were performed on 170 of the above cases. There was pathological evidence of CNS leukaemia in 39% of acute lymphocytic leukaemia, in 30% of acute undifferentiated leukaemia, in 39% of acute blastic crises in chronic myeloblastic leukaemia, and in 19% of acute myeloblastic leukaemia. This study also shows that the involvement of the nervous system was greater than was demonstrable during life. The study also showed that neurological involvement appeared to be a chronologically cumulative process with a hazard rate, or probability risk, of approximately 0.8% of patients per month early in the disease course, and of nearly 4.0% of patients per month after 3 years of disease. The relative sex incidence was unusual in this study; 16% of males and 7% of females had neurological leukaemia. Shaw et al. (1960) found the incidence of neurological leukaemia in adults and children to be twice as high in males as in females. However, Moore et al. (1960) found an approximately equal sex incidence in children. Hyman et al. (1965) found a slight bias towards a higher female incidence; 32% females, and 23% in males in a study of children. The variations of sex incidence may well be due to the varying size of different studies, of differing age structure as well, and seem in truth of no fundamental significance.

Reske-Nielsen et al. (1974) found in a study of adults and children pathological evidence of neurological leukaemia in 59% of acute lymphoblastic leukaemia (whereas in contrast there was clinical evidence of this in 15% of the same cases), in 26% in other acute forms of leukaemia, and in 84% of chronic leukaemia. Dawson et al. (1973) found roughly similar involvement in adults, 58% in acute lymphoblastic leukaemia, and 17% in acute granulocytic leukaemia.

Wolk et al. (1974) showed that adults who had developed leukaemic invasion of the CNS, had had leukaemia for longer than those patients

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without neurological involvement. The median survival times were 60 weeks for those with neurological problems and 20 weeks for those without, respectively. This was attributed to the association between survival and a beneficial chemotherapeutic response. It was also noted that the older the patient, the lower the incidence of neurological leukaemia. This would seem somewhat parodoxical and is at the moment hard to explain. These studies just referred to agree in major respects with many others. Pinkel et al. (1971) reported that 83% of children whose disease was controlled by therapy nevertheless went on and developed neurological leukaemia. Evans et al. (1970) studied 209 children. The overall neurological involvement was 51%; comprising 56% of acute lymphocytic leukaemia, and 25% of other types of leukaemia. Central nervous system leukaemia developed at the rate of 3.8% of patients per month during the first 2 years of the disease, and thereafter at the rate of 2% of patients per month. Again, longer duration of the disease predisposed to the development of CNS leukaemia. The median survival of cases that had neurological involvement was 21 months, in contrast to 13 months in those without. However, median survival after the first episode of neurological leukaemia was only 7.5 months (range, 0–46 months). Evans et al. (1970) also noted, in the course of prolonged studies in children, a rise in the incidence of neurological leukaemia from 3 to 40% between 1948 and 1960.

The further course of the disease is punctuated by recurrent episodes of neurological involvement in both adults and children. Hyman et al. (1965) found no definite correlation between recurrence and any one particular therapeutic regime. Neurological leukaemia could occur as the first symptom of leukaemia – preceding haematological and general symptomatology – although this is uncommon (Hyman et al. 1965; Levine et al. 1973; Staffansson and Rask 1973; Pochedly 1975a). Occasional cases in these studies actually developed neurological symptoms before there was detectable abnormality in either the peripheral blood or the bone marrow. This situation can be the cause of considerable diagnostic difficulty. Several such cases suffered from undifferentiated stem cell leukaemia (Pole 1973). About one-third to one-half of children develop CNS leukaemia whilst they are in complete haematological remission (Evans 1963; Pochedly 1975a). When neurological involvement occurs, the case must be regarded as being in relapse, irrespective of the haematological status (Shaw et al. 1960). Remission is interrupted by neurological involvement as frequently as by haematological relapse (Evans 1964; Nies et al. 1965; Bergevin 1975). Also, CNS relapse may occur during an haematological relapse (Shaw et al. 1960).

Hyman et al. (1965) studied 59 patients to find their haematological status at the time of an episode of neurological involvement. At the onset of neurological complications in 32 episodes the systemic disease was in complete remission, in 34 episodes the systemic disease was in a state of moderate relapse, and in 18 episodes it was in complete relapse. The bone marrow was examined at the onset of 109 episodes of neurological relapse and was normal in 58 cases, showed moderate leukaemic change in 9 cases, and marked leukaemia in 42 cases.

The latent period from the time of diagnosis of leukaemia to the time of CNS involvement varied between 9 and 14 months (Haghbin and Zuelzer 1965; Aur et al. 1971). As a simple approximation, the rate of development of neurological leukaemia is roughly 50% of patients after 18 months of disease duration and 75% after 4 years duration. Multiplicity of attacks of neurological disease seems to be the rule. In children, individuals had about three attacks, with a range of from 1–14 attacks per child; a similar frequency of attacks is seen in adults.

In conclusion, in both adults and children suffering from leukaemia, CNS involvement is common, and is being discovered more frequently due to an increase of diagnostic vigilance. It occurs in probably over one-half of all patients seen, and develops at the rate of about 2–4% of patients per month with 50% involvement after 18 months disease duration. It is commoner in acute lymphoblastic leukaemia. It can develop during remission, or during any phase of activity of the systemic disease process, and may or may not be accompanied by clinical symptoms or signs. It is seen in more patients with leukaemia of longer relative duration, but once it has developed it is

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associated with a considerable reduction in survival therafter.

It is considered that leukaemic cells find sanctuary within the CNS, perhaps sheltered to some extent from immune attack, and also partly shielded by the blood-brain barrier from some chemotherapeutic agents – although of course not from all such drugs.

MENINGEAL LEUKAEMIA

Leukaemia frequently involves the CNS producing a clinical syndrome of mixed signs, suggesting both the presence of raised intracranial pressure and meningism. Often there are no signs suggesting the presence of a focal disturbance or space-occupying lesion, and where local functional impairment occurs it is often of a type known to be associated with raised pressure – a 'false localising' sign such as a IIIrd or VIth cranial nerve palsy. Various terms are employed by different authors: meningeal leukaemia, leukaemic meningitis, and raised intracranial pressure. There are no real objections to anyone of these but it is probably best to use the descriptive term meningeal leukaemia. The presence of leukaemic infiltration of the arachnoid has been discussed previously; in addition to this there is extensive involvement of the dura in 70% of patients with lymphocytic leukaemia and in 59% of patients with myelocytic leukaemia, it being commoner amongst children – doubtless a reflection of the predominance of lymphocytic leukaemia in the young. Arachnoid infiltration was found in 30% and is also commoner in the lymphocytic form and in children (Moore et al. 1960).

Most clinical symptoms and signs are common to all cases but there are many variations seen in individual cases. Headache, drowsiness, vomiting and papilloedema are the major features. Diplopia, strabismus, blurring of vision, and blindness are commonly reported. The IIIrd and VIth cranial nerves are commonly involved. The IInd to VIIth cranial nerves are also frequently involved. Vertigo, convulsions, proptosis, neck stiffness, hydrocephalus and coma are somewhat less frequent (Wells and Silver 1957; Pierce 1962; Hyman et al. 1965; Nies et al. 1965; Bergevin 1975). In this clinical setting, elevation of the cerebrospinal fluid (CSF) pressure occurs in 80–90% of cases. As discussed in detail in the previous section, such complications can occur in association with systemic full remission, partial remission, and complete relapse, and at virtually any stage of the systemic disease. With increasingly effective therapy it is common to find patients who have had several episodes in the course of their disease. The diagnosis is established by the consideration of the entire clinical picture occurring in a patient who is known to be suffering from leukaemia. The essential clinical features must be headache, vomiting, papilloedema and other nonspecific signs, such that there is no evidence strictly explicable by the presence of a structural lesion in one particular anatomical site.

The following investigations have proved of value in assessing the problem. Plain X-rays of the skull in children show widening of the sutures. The dorsum sellae is occasionally thinned (Sansone 1954; Pierce 1962). Pole (1973) reported erosion of the left sphenoidal ridge and lateral orbital margin; Pochedly (1975a) noted occasional increased digital markings of the skull in infants. The skull circumference enlarges (Sullivan 1957). The electroencephalogram was examined in 36 patients and 27 were abnormal (Hyman et al. 1965). There were, not surprisingly, no diagnostic features. The confirmation of the diagnosis is by examination of the CSF. It might be considered curious that a clinical syndrome produced by raised pressure can be safely demonstrated by lumbar puncture. As yet there are no reports of pressure coning as a consequence of lumbar puncture. This is a consequence of elevation of pressure without, however, structural distortion and shift, or a local space-occupying lesion. The CSF pressure is nearly always elevated. The cell count varies from 13–3,000/cu. mm, median, 167/cu. mm. The pressure was in the range 135–700 mm water, median, 375 mm. The CSF protein level was above normal (25 mg/100 ml in children) in 54%, range, 7–106 mg/100 ml. The median CSF sugar was 50 mg/100 ml, range, 15–78 mg/100 ml. In eight cases out of 13 (60%) the CSF sugar levels were below one-half of the simultaneous blood sugar (Pierce 1962). Case reports by numerous other workers demonstrate similar findings. The cell types observed are predominantly the type seen in

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