NEUROMETABOLIC DISORDERS IN CHILDHOOD

Proceedings of a Symposium

NEUROMETABOLIC DISORDERS IN CHILDHOOD

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EDITED BY

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PREFACE

The motto of the University of Sheffield, 'Rerum cognoscere causa', which is taken from Virgil, may be translated to read, "To discover the cause of things". This is very appropriate for this symposium. The discovery that metabolic disorders cause some of the severe neurological diseases of childhood is changing the future outlook for those children who suffer from these conditions. This is an exciting and rapidly developing field of medical endeavour which involves several scientific disciplines, such as biochemistry, neurology and paediatrics. Our purpose in holding this symposium was to collect together information about the neuro-metabolic disorders, and to present this to clinicians as a working guide of the present state of our knowledge. This publication will, we hope, remain as a testimony of our efforts at the present time, but we realise that much that is written here will be modified and overshadowed by future developments. It is our sincere hope that these advances will occur soon, and if these papers have helped to hasten them along, then we shall feel our labours justified.

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INTRODUCTION

R. S. ILLINGWORTH

The interest in neurometabolic conditions is now so widespread that the number of known neurometabolic conditions is ever increasing, and it would be extremely difficult to prepare a complete list of them.

The subject is such a vast one that it is obvious that a one-day symposium on neurometabolic conditions could not hope to do more than touch the fringe of the subject. Nevertheless, a one-day meeting in Sheffield on May 31st, 1963, did cover many important aspects of current research. Experts from many parts of the country collected together and took part in the discussions. This volume is the product of the meeting. It is hoped that it will be of interest to many who are interested in the biochemical aspects of disease, and that it will provide a stimulus to further research.

1

THE BIOCHEMICAL ASPECTS OF CHILD NEUROLOGY

K. S. HOLT

IN recent years advances have been made in biochemistry which are as great as those in any other branch of medicine, and many of the stimulating advances in this field apply to child neurology. Before attempting a brief review a word must be said about the nature and scope of child neurology.

Child neurology is an important part of developmental medicine. It is the study of the developing nervous system which is pursued in order to understand how the clinical picture is modified by growth and maturation. The fact that one is dealing with a changing situation has to be kept in mind all the time. For example, a concept which is useful in dealing with the static mature nervous system, namely that clinical signs may be the result of the release of lower level activity following destruction of the higher centres, has to be applied cautiously and less rigidly when considering a nervous system which has not yet achieved its full complexity.

Undoubtedly, many factors must influence the developing nervous system, and biochemical factors are some of the most important ones. The nervous system, like all growing tissues, is dependent upon chemicals for its adequate development, and it is affected by disturbances of them. The response of the nervous system to biochemical disturbances varies with its maturity, a subject which is discussed by Richter (1955). Another reason why biochemical factors are important in child neurology is that most of the metabolic errors which affect the brain are first encountered in the early years of life. This is a vast subject and I do not think that I am alone among clinicians in feeling bemused by the many recent developments. I have found it helpful to divide the biochemical problems of child neurology into two groups. Group I consisting of the problems which arise from a disturbance of the physiological environment of the nervous tissue, and Group II consisting of the problems which result from toxic substances.

GROUP I

DISTURBANCES OF PHYSIOLOGICAL ENVIRONMENT

The conditions in this group have the following characteristics.

(*a*) The chemicals concerned are usually simple ones of low molecular weight.

(*b*) The disturbances are not unduly rare.

(*c*) The disturbances are usually acute, temporary, and may not leave any residual damage.

(*d*) A gradation of clinical effects may occur depending upon the extent of the physiological disturbance.

(*e*) The disturbances may be due to a change in the absolute level of the substance concerned, or due to an exceptional rate of change of this level.

(*f*) Early, pre-symptomatic detection of these disturbances is not feasible.

The conditions in this group are caused by disturbances of the following substances.

Oxygen

Oxygen is one of the two vital energy sources of the brain. Glucose is the other one. It is surprising that, despite the fact that oxygen is so essential to the brain, there is no reservoir for emergency use, and at any moment the oxygen available in the brain would last only a few seconds (Kety, 1955). Only the presence of anaerobic metabolism in the very immature brain protects it from really devastating damage by anoxia.

The clinical picture of anoxia with restlessness, rigidity, convulsions, coma and death is too well known in paediatric practice to need further discussion.

The possibility that exposure to excessively high concentrations of oxygen is not altogether innocuous cannot be dismissed. It has been reported, for example, that it increases the susceptibility to convulsions (Gibbs, Foss & Gibbs, 1955).

Carbon dioxide

The useful actions of carbon dioxide on the brain were summarised by Lennox & Lennox (1960) as follows.

'Carbon dioxide is not an inert gas, nor a poisonous one. It is most useful in assisting the brain to function normally; carbon dioxide penetrates cell barriers 20 to 30 times more rapidly than oxygen. It acts quickly to adjust an acid-base imbalance, and is much more effective than oxygen in altering cerebral circulation, in stimulating respiration, and in controlling tetany, hiccups, and neuromuscular reflexes.'

However, in contrast, the clinical picture of over-ventilation which produces a rapid fall of the arterial carbon dioxide, is well known in childhood. It consists of increased tendon reflexes, tetany, and convulsions.

Glucose

Glucose is the other major source of energy for the brain. When the blood sugar level is low convulsions frequently occur. The relationship between the blood sugar level and the occurrence of convulsions is not a close one, however, and other factors determine whether or not convulsions will occur at any particular blood sugar level. Two of these factors are:

(*a*) the age of the patient, neonates, for example, are resistant to quite low blood sugar levels, and

(*b*) the rate of fall of the blood sugar, the more rapid the fall the more likely will convulsions ensue.

Much has been written recently about the different types of hypoglycaemia which the clinician must suspect in any infant or child with convulsions. The history may be suggestive. Three important points are the following.

(*a*) Symptoms due to excess adrenalin, such as pallor, sweating, trembling.

(*b*) Attacks occurring only in the fasting state.

(*c*) Attacks occurring regularly one to three hours after meals.

The absence of a suggestive history does not exclude the need to consider hypoglycaemia further. The blood and cerebrospinal sugar levels estimated at the time of the convulsion may be abnormal. The finding of a sugar level of between 10 and 30 mg./100 ml. in an otherwise normal cerebrospinal fluid was the first indication that hypoglycaemia was the cause of the convulsions in several children seen at Sheffield Children's Hospital. Hypoglycaemia cannot be excluded as a cause of convulsions in a child until it has been demonstrated that hypoglycaemia (< 50 mg./100 ml.) does not occur in the following stressful circumstances.

(*a*) After fasting for 24 hours.

(*b*) Up to four hours after an oral glucose tolerance test.

(*c*) Up to one hour after a casein tolerance test.

(In the casein test for leucine sensitive hypoglycaemia, Millichap (1960) suggests that the blood sugar level should fall to half the fasting level for the test to be positive.)

When hypoglycaemia is diagnosed further information can be obtained by noting the response of the blood sugar to insulin and adrenalin. The different types of hypoglycaemia are summarised below in an abbreviated form.

(*a*) Hyperinsulinism—rare; frequent convulsions; low fasting blood sugar; slow rise of blood sugar after glucose; poor response to insulin. Treatment: corticotrophin or partial pancrectomy.

(*b*) Reactive hypoglycaemia—common; fasting blood sugar normal; blood sugar falls two to four hours after meals when attacks occur; response to insulin and adrenalin normal. Treatment: dietary; decrease carbohydrate and increase protein intake.

(*c*) Fasting hypoglycaemia—common; blood sugar level in normal range unless fasting continued for 24 hours when level falls below 50 mg./100 ml. and attacks occur; insulin sensitive, but may show poor response to adrenalin (Broberger, Jungner & Zetterström, 1959). Treatment: avoid long fasts; ephedrine.

(*d*) Leucine sensitivity (Cochrane, Payne, Simpkiss & Woolf, 1956)—

rare; fasting blood sugar normal; blood sugar falls half to one hour after protein containing meals when attacks occur; insulin and adrenalin response normal. Treatment: reduced protein intake.

Occasionally convulsions continue despite correction of the hypoglycemia. It is then important to consider whether cerebral anoxic damage sustained in earlier attacks might be the cause (McKendrick, 1962).

Sodium

Sodium is important because it is thought that the threshold to seizures is primarily dependent upon the ratio of intra- and extra-cellular sodium (Woodbury, Koch & Vernadakis, 1958). Neurological symptoms occur with both hypo- and hyper-natraemia.

Hyponatraemia increases the tendency to convulsions. It may predispose to the occurrence of febrile convulsions and it may reduce the response to anticonvulsant drugs (Millichap, 1960). The critical serum sodium level is about 120 m.Eq./l. and when the level falls below this convulsions frequently occur, but the effects are temporary and can be reversed by increasing the intake of sodium.

Hypernatraemia (serum sodium over 150 m.Eq./l.) is associated with increased muscle tone and decreased reflexes and in advanced cases convulsions and coma occur. Opisthotonus was a prominent feature in a recent case and the clinical picture simulated meningitis closely. Hypernatraemia is thought to damage the cell barrier and certainly this condition is more often followed by permanent damage than is hyponatraemia.

A special cause of hypernatremia is diabetes insipidus (Waring, Kajdi & Tappan, 1945; Kirman, Black, Wilkinson & Evans, 1956) where the low specific gravity of the profuse urine is in marked contrast to the serum electrolyte concentration. Failure to recognise and to treat this condition in infancy results in mental retardation.

Calcium

Calcium probably produces disturbances by affecting cell permeability and upsetting the sodium balance. Both high and low levels are associated with symptoms. The tetany of hypocalcaemia (<8g./100 ml.) is well known, and the association of mental retardation with hypercalcaemia (>12g./100 ml.) makes early treatment important. Mental retardation has also been reported in association with the various rare disorders of calcium metabolism.

Magnesium

Brief mention must be made of magnesium, which when it is reduced excessively causes a picture similar to tetany, with muscle tremors, weakness, depression and ataxia. This is particularly liable to occur after severe gastroenteritis (Back, Montgomery & Ward, 1962).

Acetyl choline, gamma aminobutyric acid and pyridoxine

Any discussion of the physiological environment of the nervous system must include mention of the two substances, acetyl choline and γ aminobutyric acid. Acetyl choline has long been considered to be a stimulating agent in the central nervous system and when it is present in increased concentration it produces convulsions (Hebb, 1957; Tower, 1960). The importance of γ aminobutyric acid was appreciated more recently (Elliott & Jasper, 1959; Roberts, 1960). It is thought to be the key to the inhibitory mechanisms of the brain. Its formation from glutamic acid is controlled by the co-enzyme pyridoxine (vitamin B_6), and when this is deficient convulsions occur. That they do occur was clearly impressed upon clinicians almost 10 years ago when an epidemic of convulsions in babies in America was traced to a deficiency of pyridoxine in their synthetic feeds (Bessey, Adam, Bussey & Hansen, 1954; Coursin, 1954; Molony & Parmalee, 1954). Since then the relationship between pyridoxine and infantile convulsions has been clarified by Coursin (1960) who, among others, divides the cases into the following three groups.

(*a*) Due to a deficient intake of pyridoxine.

(*b*) Due to excessive pyridoxic acid formation.

(*c*) Due to excessive needs for pyridoxine (pyridoxine dependency) (Hunt, Stokes, McCrory & Stroud, 1954).

As a result of this increased knowledge it is now the usual practice to carry out a therapeutic trial of large doses of pyridoxine (10-20 mg. daily) in any infant with convulsions of unknown aetiology who does not respond promptly and completely to anticonvulsant drugs.

GROUP II. DISTURBANCES DUE TO INTOXICATIONS

The conditions in this group can be produced in several ways, as follows.

(*a*) From an internal source of toxic substances.

(i) by derangement of normal metabolic pathways such as occurs in liver and kidney failure,

(ii) by the presence of abnormal metabolic patterns such as occur in the inborn errors of metabolism.

(*b*) From an external source of toxic substances, for example, lead poisoning.

The conditions due to inborn errors of metabolism are of particular interest at present, and their characteristics are as follows.

(*a*) The substances concerned are complex organic chemicals.

(*b*) The conditions are uncommon.

(*c*) The conditions are genetically determined and may occur in siblings.

(*d*) Involvement is usually 'all or none', and the gradation of clinical effects seen in Group I conditions does not occur to anywhere near the same extent.

(*e*) The biochemical disturbance is permanent. It is present before the onset of clinical manifestations so that early, preclinical detection is possible.

(*f*) The clinical effects may be reversible. This is shown by the response to treatment in phenylketonuria.

(*g*) Most of the conditions have a diffuse effect upon the nervous system with mental retardation and convulsions being the principal features. Wilson's disease with a more localised brain lesion is an exception. (In contrast also, is the situation in hyperbilirubinaemia where specific localised damage is produced.)

It is not proposed to describe the individual conditions in this group because they are described in the later papers. Instead the clinical approach will be discussed.

Diagnosis of the established case

Diagnosis is made easier by the fact that the different conditions present a fairly constant clinical picture and time of onset. Examples are shown below.

Age period	*Condition*	*Clinical features*
Neonatal .	Galactosaemia (von Reuss, 1908)	Vomiting, hepatomegaly, jaundice, ascites, oedema, convulsions, cataracts.
	Maple syrup disease (Menkes, Hurst & Craig, 1954)	Absent Moro reflex, feeding difficulty, hypertonus, opisthotonus.
	Argininosuccinic - aciduria (Allan, Cusworth, Dent & Wilson, 1958)	Retardation, convulsions, ataxia, hepatomegaly, friable hair.
Infancy .	Phenylketonuria (Fölling, 1934)	Retardation, convulsions, eczema, bronchitis.
	Gargoylism (Hurler, 1917)	Facies, heart murmur, retardation, deafness, corneal opacities, hepatomegaly.
	Tay Sachs disease (Tay, 1881)	Severe retardation, retinal red spot.
Childhood .	Wilson's disease (Wilson, 1912)	Convulsions, Parkinsonism, Bulbar symptoms, corneal pigmentation.
	Hartnup disease (Baron, Dent, Harris, Hart & Jepson, 1956)	Pellagra like skin rash, ataxia, nystagmus, retardation.

(Later references to these conditions appear in Dr. Stern's paper.)

Our understanding of the mechanisms of these diseases and the planning of a logical approach to the biochemical diagnosis has been clarified by the writings of Professor Dent (1957), to whom we owe so much in this field. Establishment of the diagnosis can be approached in three ways, as follows.

(*a*) Demonstration of excessive quantities of the metabolites proximal to the enzyme block occurring in the urine, blood or cerebrospinal fluid. Phenylketonuria is diagnosed in this way.

(*b*) Demonstration of a deficiency of the metabolites normally present distal to the enzyme block. The hypoglycaemia of glycogen storage disease is explained in this way.

(*c*) Demonstration of the fault in the enzyme itself. Galactosaemia is the best example of this.

Although the perfection in diagnosis is to demonstrate the fundamental deficiency, namely the enzyme fault, this can seldom be achieved as yet in these conditions. Apart from the specific enzyme systems, some disturbance of the other enzyme systems may be found in these conditions, a subject which was reviewed recently by Aronson (1960). He reported, among other things, that great care was needed to obtain reliable results in enzyme estimations; that in degenerative conditions of the brain the rate of change at any one time might be too slow to produce a significant rise in the enzyme level; and that in Tay Sach's disease the glutamic oxalacetic transaminase level was exceptionally high in both the serum and cerebrospinal fluid, and that these changes antedated the onset of clinical symptoms.

Detection of the pre-clinical case

One of the characteristic features of the conditions in this group is that the biochemical defect is present from the beginning and often before the appearance of clinical symptoms. It should be possible, therefore, to detect affected children in this pre-symptomatic period by appropriate chemical tests. It is the paediatrician's task to detect the patients in this early stage. Dobbs (1962) expressed this need strongly when he said 'by the time we need to call in neurologists we have failed, either through our own fault or through lack of knowledge on the subject'. The values of early detection are as follows.

(*a*) To establish the diagnosis, and so to help to guide the parents about the prognosis and future pregnancies before too long a time has passed. It is not now justified to give advice about future pregnancies in the case of children with convulsions or retardation until the fullest biochemical assessment has been made.

(*b*) To enable treatment, when this is possible, to be started early. The value of this has been amply demonstrated in phenylketonuria.

(*c*) To establish that the condition is not present in certain groups of individuals, especially in

(i) the siblings of affected children,

(ii) children with suggestive clinical features,

(iii) children for adoption.

In connection with the biochemical screening of babies for adoption all will agree that the urine must be tested to exclude phenylketonuria. But should it stop there? Why not examine the urine for urinary mucopolysaccharides to exclude gargoylism, and the cerebrospinal fluid for glutamic oxalacetic transaminase to exclude Tay Sach's disease? It is ironical that a case can be made out for the high powered biochemical screening of these babies when not all of them even have an adequate paediatric and developmental examination before completion of the legal formalities.

The widespread screening of normal infants is of doubtful value because the conditions are rare and very many negative results are recorded and errors can easily occur. Even the testing of populations likely to have a high incidence of these metabolic abnormalities, for example, mentally defective children, reveals only a few cases, as was shown by Carson & Neill (1962) and others. It is important that we decide which children to test, when to test them, how to test them, and which conditions to test for, so that a clear approach can be made in this field.

The clinician and the biochemist

The rapid advances of recent years have created a situation in which it is easy for the clinician to panic and to order biochemical tests with gay abandon in the hope that one of these conditions might be found. We must learn the limitations of the biochemical tests which are easier to request than to perform. They are expensive and time consuming, and they also usually only show the state of one chemical at one particular moment. The need to ensure that the biochemical tests are chosen carefully, carried out at the right moment, and in the correct way, means that the clinician and biochemist should be very close partners in this work at all times. It is therefore a thrill and an honour to see so many experts from both fields gathered together today for this symposium.

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BIOCHEMICAL ASPECTS OF DISORDERS OF MOOD

F. A. JENNER

THE more I have thought about the presentation of this paper the more conscious have I become of the major difficulties which are involved. Firstly, the symposium is devoted to disorders in children, and I have never worked with children. Furthermore, despite frequently raised hopes and hypotheses, it has to be stated clearly that the relevance of biochemistry to the aetiology of the major psychoses has still to be established. Indeed, one of the achievements of clinical psychiatry has been the separation in terms of the clinical signs and symptoms of the organic dementias and toxic confusional states from the so-called functional psychoses. In the first group physical changes of aetiological significance will probably be found in life of at post mortem. In the second group nothing very significant to which an aetiological nature can be attributed is likely to be found, despite the most extensive clinical laboratory facilities. Furthermore, psychoanalytical writers and other psychodynamicists have presented plausible, although rarely scientifically established theories, relating to the aetiology of most mental disorders. Even if practitioners in general find most psychodynamic theories exaggerated in the explanation of schizophrenia, few would deny the enormous environmental, and interpersonal factors affecting our moods. In particular, clinical psychiatry has had difficulties in separating the so-called endogenous depressions from the so-called reactive depressions, that is, in distinguishing the depressions in which neurotic psychodynamic responses can be said to play an important role, from those in which these factors are of less significance. In one of his most distinguished essays 'Mourning and Melancholia', Freud (1925), by implication, illustrates this difficulty, and shows the similarity between excessive results of bereavement and those of endogenous depression. He, and also Abraham (1942), postulated that depression, for example, is often the result of loss of a loved object towards which the individual feels ambivalence. Many modern clinicians feel that this is a helpful concept, and it is attested by the weight of their clinical experience (Pottash, 1962). Such psychodynamic formulations are useful hypotheses to test in terms of the problems presented by each patient as an individual. Certainly, psychodynamic factors, despite their complexities, must not be overlooked in any study of mental disorders and human behaviour, but they are not the whole story. There are other factors. This is made quite clear even if only in a limited number of cases.

My contribution to this symposium will be devoted to considerations