

Cretinism: Early Diagnosis and its Relation to Mental Prognosis

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Raiti, S., and Newns, G. H. (1971). *Archives of Disease in Childhood*, **46**, 692. **Cretinism: early diagnosis and its relation to mental prognosis.** A total of 141 cases of hypothyroidism diagnosed within the first two years has been reviewed. The best mental development was achieved when treatment was begun within the first three months of life. At this time hypothyroidism presents mainly with symptoms—usually feeding difficulty, constipation, and lethargy, while the classical physical signs are less obvious than later.

Cretinism was the first form of mental deficiency to become treatable and largely preventable (Cranefield, 1962). However, in order to achieve the best mental prognosis, cretinism must be diagnosed early, preferably before the third month of life. In this neonatal period, the symptoms of thyroid deficiency are often more prominent than are the clinical signs. The purpose of this report is to evaluate the features which permitted diagnosis within the first three months of life, and to compare the mental level achieved in this group with that of patients diagnosed later.

Review of Cases

A total of 141 cases first diagnosed and treated at this hospital was reviewed. There were 106 females and 35 males (3:1 ratio). 9 cases were diagnosed during the first month of life, 11 during the second month, 20 during the third month, 23 between the fourth and end of the sixth month, and 78 between the seventh and twenty-fourth month of life.

The presenting symptoms and signs and their frequency are set out in Table I. Constipation was the most common symptom. Feeding was often difficult and slow, occasionally continuing up to the time for the next feed. The babies were often lethargic, well behaved, cried little, and slept most of the time. Respiratory symptoms varied from a 'blocked nose' associated with distress during feeds, to frank cyanosis suggestive of congenital heart disease.

The typical facies of cretinism was recognized in 109 cases but only in 25% of those cases diagnosed before

TABLE I
Symptoms and Signs Present at Age When Diagnosis was Made

Symptoms and Signs	0-3 months	4-6 months	7-24 months	Total
Total number of cases	40	23	78	141
<i>Symptoms</i>				
Constipation	26	11	46	83
Feeding problems	24	14	27	65
Lethargy	22	11	24	57
Respiratory symptoms	12	3	1	16
<i>Signs</i>				
Umbilical hernia	27	15	34	76
Enlarged or protruding tongue	26	21	78	125
Facies	10	21	78	109
Neonatal jaundice	11	4	12	27
Altered cry	9	7	16	32

3 months of age. An enlarged, protruding tongue and an umbilical hernia were the most common features in the 0 to 3 month age group. Jaundice was present in 25% of the cases diagnosed in the first three months. This was noticeable at 3-4 days of life and often persisted up to 2 months of age. Other signs included dryness and mottling of the skin, carotenaemia, and supraclavicular pads of fat.

Investigations. In the patients diagnosed before 1 year of age, 27 had serum cholesterol values of less than 220 mg/100 ml, 17 had values of 220-300 mg/100 ml, and 7 had levels above 300 mg/100 ml (normal laboratory range after 1 month of age was 100 to 220 mg/100 ml). The PBI was measured initially in 33 cases and varied between 0.2 and 3.5 µg/100 ml. The bone age at the left wrist was delayed in all cases, and in younger patients it was also delayed at the knee and

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ankle. Radioactive iodine uptakes were not measured in most cases. The ECG before therapy in 55 cases showed a normal pattern in 36 patients, and changes consistent with hypothyroidism in the other 19. EEG before therapy was recorded in 19 cases and showed small amplitude and/or slow activity in 6 cases: 4 of these 6 cases were less than 3 months of age but the IQ of only one of them was subsequently found to be less than 90. 2 of the patients who presented after 7 months of age had normal EEGs but IQs below 90.

The IQ was measured at varying ages in 56 cases (Table II). When tested, 7 were 5 years old or less, 46 were 6 to 10 years, and 4 were over 10 years of age. 14 of 19 cases where treatment was begun within the first three months of life had IQs above 90. 4 of the 5 whose IQ was below 90 began treatment during the third month of life. Only 33% of the patients first treated between the fourth and the sixth month, and 40% of those first treated after six months of age, had IQs above 90.

TABLE II
IQ in Relation to Age in 56 Cases

Age When Diagnosis Made	Number of Cases*	IQ	
		90 +	90 -
(a) Before end of 3 months of age	40 (19)	14	5
(b) Between 4 and end of 6 months of age	23 (12)	4	8
(c) Between 7 and end of 24 months of age	78 (25)	10	15
Total number of cases	141 (56)	28	28

*Figures in brackets indicate number tested.

Associated features. 4 patients developed convulsions and required anticonvulsive therapy. 4 patients were deaf. 1 child had Werdnig-Hoffmann disease; he was subsequently lost to follow-up.

Six children died, 3 being possibly related to starting therapy: 1 died on the day after treatment was begun; the second died after tube-feeding two weeks after starting therapy; and the third developed diarrhoea and vomiting 2 weeks after therapy began, and died suddenly despite intravenous therapy. Of the other 3 deaths, 2 died from associated congenital heart disease and 1 had bronchopneumonia.

Familial incidence. In 4 families, affected sibs were found. In the first (the parents being first cousins) both of the 2 children were affected. In the second and third families, there were 2 affected and 1 normal child. In the fourth family, there were 2 athyrotic cretins and 3 normal children. None had features of an enzymatic defect, or a maternal history of either Hashimoto's disease or spontaneous myxoedema.

Discussion

In reviewing the cases for early diagnostic clinical features, it was apparent that *symptoms* of

hypothyroidism were recognizable before the classical signs. The most constant symptoms were constipation, feeding problems, and lethargy or inactivity. Respiratory symptoms were found in only 11% of all cases in contrast to 75% of patients described by Lowrey *et al.* (1958). Neonatal jaundice was found in about 20% of cases. The earliest physical signs included an enlarged and protruding tongue and an umbilical hernia.

The best mental prognosis was achieved in those patients whose treatment was started during the first three months of life (i.e. in 14 of 19 cases subsequently tested). These results conform with those reported by such other investigators as Smith, Blizzard, and Wilkins (1957) (7 of 15 cases or 50%), Andersen (1961) (2 of 4 cases or 50%), and Man, Mermann, and Cooke (1963) (5 of 8 cases or 62%). Patients with lower IQs are believed to have longer-standing intrauterine thyroid deficiency.

The prenatal and early postnatal period is critical for brain development. At the 8th fetal month, the ratio of cerebral tissue to total brain weight is higher than at any other time of life, and at birth the weight of the brain is 25% of the total adult brain weight (Carr *et al.*, 1959). Half of the post-natal brain growth is completed by 6 months of age (Pickering and Fisher, 1958). Maternal thyroxine does not cross the placenta in sufficient amounts to protect the fetus. Tri-iodothyronine if given in larger quantities will cross the placenta in the majority of cases (Raiti *et al.*, 1967).

The early diagnosis of cretinism is, therefore, suggested by the symptoms outlined and is confirmed by laboratory tests. Skeletal x-ray provides the most useful test. Epiphyses at the knee and ankle usually appear during the seventh intrauterine month, and these centres should be present at birth (Dorff, 1936; Wilkins, 1962). X-ray of the wrist is helpful after the 3rd to 6th month of life. Epiphyseal dysgenesis is found in hypothyroidism of longer standing. The diagnosis can be confirmed within 24 hours by demonstrating a low radioactive iodine uptake both over the thyroid and submental region (to exclude a lingual thyroid). Blood tests for thyroid deficiency (e.g. PBI) should be performed but therapy can be started before the results are received. The serum cholesterol is an unreliable guide of thyroid deficiency during the first year of life. Tests such as the *in vitro* red blood cell uptake of ¹³¹I L-tri-iodothyronine have also proved to be an unreliable indication during childhood (Sabeh *et al.*, 1964). EEG changes are not reliable guides for mental prognosis (Andersen, 1961; Federman, Robbins, and Rall, 1958).

L-Thyroxine is the drug of choice for the treat-

ment of cretinism. During the first year of life, 0.1 mg per day usually suffices, and after that time the dose can be increased to 0.1 to 0.3 mg per day, as determined by clinical progress, bone age, and periodic confirmatory blood tests. The tablets need only be taken once daily since the drug has a long half-life. Initially, therapy should be started with 0.025 mg daily and the dose increased by this amount every four days so that a dose of 0.1 mg daily is given by the end of the second week. If there is initial evidence of cardiac complications, half doses should be given at these intervals, i.e. 0.0125 mg initially and increased by this amount every four days so that by the end of four weeks, the dose of 0.1 mg daily is given. Parents should be warned that, with therapy, the babies will lose weight (loss of increased body water) and may also lose their hair, but that both these changes will be reversed with continued therapy.

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