Clinico-pathological Study of Thymic Dysplasia

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In a recent necropsy study of a thousand cases in which adequate amounts of thymus gland were available, Berry (1968) found a large number of abnormalities. Most of these were related to the lymphocyte population and in some cases apparently resulted from the exhibition of cytotoxic drugs or steroid hormones. In 17 cases epithelial abnormalities were found, these glands showing lymphocyte depletions associated with absence of, or reduction in, the number of Hassal’s corpuscles to less than 5% of the normal numbers for the age. The normal data were derived from Boyd (1932).

In all 14 of these 17 cases in which adequate material remained for examination, other abnormalities of lymphoid organs were found. The clinical histories of these 17 have been reviewed, and in 14 where adequate data were available, a clinico-pathological correlation was attempted. The clinical and pathological findings are summarized in Tables I and II: photomicrographs of classical thymic, lymph node, and appendiceal abnormalities are shown in Fig. 1, 2, and 3.

**Clinical Features**

In 12 of the 17 patients the clinical history and findings were similar, the salient features being diarrhoea, failure to thrive, and recurrent infections (Cases 1–4, 6–9, 11–14).

All but one (Case 15—congenital rubella) had birthweights greater than 2721 g. (6 lb.). Most did well initially, the exceptions being those patients with the rubella syndrome who never thrived (Cases 15–17). At death, all but 2 (Cases 5 and 10) had weights below the 3rd centile; these 2 were atypical in other respects and are described separately.

The age of onset of symptoms was between birth and 8 months. An apparent relation between age at onset and age at death was found, with a less rapid course in those in whom the onset of symptoms was late. A history of similarly affected sibs (Cases 2, 7, and 13) and cousin (Case 7) was found in 3 cases. Because of this history these patients had been investigated before the onset of symptoms.

Of the 17 patients, 12 were male.

**Cases 1–4, 6–9, 11–14.** The clinical features in this group of 12 cases were strikingly similar. Diarrhoea was a dominant feature, being the presenting symptom in 6, and was usually persistent. Repeated bacterial culture of the faeces failed to reveal pathogens, but terminal monilial infection was found in 4. In all patients, other causes for malabsorption were looked for but not found. However, in 5 (Cases 2–4, 6, and 9) disaccharide intolerance was present, temporary improvement resulting when the offending sugars were withdrawn from the diet. Faecal fat estimations were normal in those patients studied (Cases 2, 6, and 9). In a few patients, the diarrhoea followed all foods, and long-term intravenous feeding was necessary. The failure to thrive was marked after the onset of diarrhoea and infections in all infants except one (Case 6), in whom it developed terminally.

In 6 patients, recurrent infections were a presenting feature, ultimately occurring in all. The sites of infection were the respiratory tract, mouth, skin, but in 4 infants (Cases 1–4) a terminal sepsicaemia occurred. The organisms most frequently responsible were staphylococci, streptococci, *Esch. coli*, and klebsiella. Monilial infections occurred later, apparently related to antibiotic therapy, and proved troublesome in most patients. In 2 infants in whom long-term intravenous feeding was necessary, candida sepsicaemia developed, one of these children having candida meningitis (Case 1). Both had received large doses of antibiotics for other bacterial infections. The candidiasis responded to therapy, but the over-all steady deterioration continued, with death at 6 and 14 months, respectively (Cases 1 and 2).

None of these children developed the common exanthemata of childhood, but many were of an age when the incidence is low. One child had been vaccinated unsuccessfully at 3 weeks of age; no complications occurred.

The age at death in these children ranged from 2 months to 3 years with a mean of 9 months.

The remaining 5 patients, where a different clinical course was present, are now described.

**Case 10.** The first-born of unrelated parents, who developed eczema at a few weeks of age. At 7 months he developed Kaposi’s varicelliform eruption after contact with herpes simplex. Virus was isolated from the lesions at 10 months and 4 years of age, but was not looked for on other occasions. Spontaneous purpura.
was noted. The child grew normally. Recurrent bouts of otitis media and pneumonia occurred throughout his life. Lymphocyte counts ranged from 1000–5000, with a mean of 2000/cu. mm. Serum proteins and electrophoresis on 4 occasions showed an increase of γ-globulin. No isoagglutinins were found. Terminally he developed acute glomerulonephritis, presenting as the nephrotic syndrome, and he died at the age of 4 years and 10 months. The cause of death was renal failure and pneumonia. The necropsy showed proliferative glomerulonephritis in addition to the thymic abnormalities.

**Case 5.** Infection was the dominant feature in this child. Extensive skin sepsis was present from the age of 1 month, healing was slow, with poor response to systemic antibiotics. Recurrent high fevers, with no apparent cause, were noted in the last few weeks of life. Weight loss and diarrhea were also noted terminally. Lymphopenia was never found. Immune globulin levels were increased, with very high IgM levels (2800% of reference normal serum). Iso-agglutinins were present. At necropsy ulceration of the small and large bowel was found, in addition to the thymic and lymphoid abnormalities.

**Cases 15, 16, and 17.** These 3 children had congenital rubella, proved by virus isolation in 2. In the other (Case 17) there was a history of maternal rubella in the first trimester of pregnancy. The child had

### Table II

**Pathological Findings**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Hassall's Corpuscles</th>
<th>Lymphocytic Depletion</th>
<th>Lymph Nodes</th>
<th>Gut, Organized Lymphoid Tissue Hypoplasia</th>
<th>Tonsillar Hypoplasia</th>
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<td></td>
<td></td>
<td>Follicles</td>
<td>Lyphocytic Depletion</td>
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</table>

Cases 13, 14, 17, insufficient material from other tissues available.

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**Note:** RNS % reference normal serum (Soothill, 1962).
multiple abnormalities including microcephaly, congenital heart disease, and bilateral hare-lip and cleft palate. Birthweights were 1360, 3175, and 4082 g. (3, 7, and 9 lb.), respectively. All these children failed to put on weight and suffered from chronic diarrhoea and repeated infections. 2 died at 3 weeks of age, the other at 4 months. Lymphopenia was not found. In 2, γ-globulin levels were measured; these were normal in 1, and in the other IgA was normal, but IgG and IgM were low.

Laboratory Findings

Lymphopenia with counts less than 1000/cu.mm. were seen in 2 patients (Cases 6 and 7). In 2 others, counts were consistently greater than 5000 (Cases 5 and 8), but in the remaining patients, though variable counts occurred, they were usually lower than expected in children of this age (Tobler and Cottier, 1958). In 4 of these, terminal counts were less than 1000/cu.mm.

Hb levels of less than 9 g./100 ml. were present in 6 children. In 2, bone-marrow examination showed

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**FIG. 1.—Thymus: typical 'glandular' pattern with absent Hassall's corpuscles. (H. and E. × 128.)**
hypocellularity with an increase of histiocytes and erythrophagocytosis. In 1 patient (Case 3, previously reported by Thompson (1967)), agranulocytosis and terminal aplastic anaemia occurred. Thrombocytopenia was a feature in 7 patients, 2 of whom had congenital rubella.

The plasma proteins were examined in all instances and serum immunoglobulins in 8. A reduction in γ-globulin was noted in 4 of the 8 patients in whom a simple protein electrophoretic strip was done. In the 8 where the immunoglobulins were measured by double gel diffusion precipitation technique (Soothill, 1962),
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IgG levels were consistently less than normal in 5, IgA levels were less than normal in 3, and IgM was less in 3 (Table 1). The ages at the time of determination were: 12–14 months (Case 1), 4 months (Case 2), 3 months (Case 3), 6 months (Case 4), 8 months (Case 5), 6 months (Case 13), 3 weeks (Case 16), and 3 months (Case 17).

Discussion

A recent review by Haworth, Hoogstraten, and Taylor (1967) added 13 cases to the growing literature on the association between thymic abnormality and immune deficiency states. That these may vary in type is shown by the reports of de Vaal and Seynhaeve (1959), Salmon and Webb (1963), and Peterson, Kelly, and Good (1964). Though the majority of our cases resemble the syndrome described by Glanzmann and Riniker (1950) and often referred to as ‘Swiss’ type α-γ-globulinaemia, there are obvious exceptions, both in the mode of expression of the defect (Cases 5 and 10) and, possibly, in aetiological terms (those cases associated with the rubella syndrome).

Our series is a retrospective one, based on a particular histological finding, and does not include detailed investigation of function. This might reveal differences in an apparently homogeneous group (Cases 1–4, 6–9, and 11–14). However, the histopathological findings emphasize the heterogeneity of structure that may accompany this uniform clinical picture.

Identification of factors responsible for any particular aspect of the clinical history is difficult. In this group all the children had done well initially, and then, after the onset of diarrhoea, failed to thrive and developed recurrent bacterial infections. The cause of the diarrhoea was not determined in any case, but all were investigated fully for possible causes of intestinal malabsorption. The disaccharide intolerance, found in the few where this was looked for, was considered to be a secondary phenomenon.

The infections were mainly of bacterial origin and, though responding partially to antibiotic therapy, tended to recur. We have found that the severe monilial infections (local or systemic) occurred after intensive antibiotic therapy. Detailed virological studies were not performed. However, the case described by Schaller et al., (1966), where there was considerable delay in eliminating Esch. coli bacteraphage from the circulation in a similar patient, suggests that this kind of study of cellular immune function would be of value. One infant in our series had been vaccinated against smallpox at 3 weeks of age; no problems occurred but the vaccination did not ‘take’. One other child developed a chronic Kaposi’s varicelliform eruption, continuing until his death 4½ years later. This child (Case 10) differed from the others in several aspects: diarrhoea was never an important symptom, and failure to thrive was not marked, his weight at the time of death being on the 50th centile. The clinical findings were suggestive of the Aldrich syndrome, with chronic eczema, thrombocytopenia, decrease of γ-globulin on paper electrophoresis, and absence of iso-agglutinins (Aldrich, Steinberg, and Campbell, 1954).

The other child with ‘atypical’ features (Case 5) presented with infections in the first month of life and thrived reasonably well until her death from pneumonia at 10 months. Lymphopenia was not present and the immunoglobulin levels measured at 9 months of age showed a marked increase in IgM and IgG; IgA was normal.

Only 2 cases in this series had lymphopenia; 8 others had varying counts, some of which were low: 2 others had consistently high counts. However, we did find that towards the end of the illness there was a tendency for the levels to fall. The presence of lymphopenia with the clinical findings described is suggestive of an immune deficiency state, but a normal or high count does not exclude it.

Hypo-γ-globulinaemia similarly does not appear to be an invariable finding. In the 8 patients where the immunoglobulins were measured, a wide range of values was obtained when compared to the normal data for different age-groups (Soothill, Hayes, and Dudgeon, 1966). IgG was reduced in 5, but high levels were found in 3, 1 of whom had 4 separate determinations. IgA was reduced in 3 and above normal in 4. IgM was low in 2, normal in 3, and higher than the adult in range 2, 1 of whom had 4 estimations (Case 1). The other child (Case 5) is described separately because of the atypical clinical course. In only 2 children (Cases 2 and 3) were all 3 immunoglobulins low; in 1 (Case 4) IgG and IgA were low but IgM was increased.

Of the 2 with congenital rubella, 1 had normal values and the other a slight reduction in IgM and IgG only. Neither showed the high IgM levels reported by other workers (Alford, 1965; Bellanti et al., 1965; Soothill et al., 1966). In 7 other patients where only paper electrophoresis of the plasma proteins was done, 4 showed low levels. Absence or gross deficiency of immunoglobulins has been found in most of the reported cases, but in some, normal levels (Nezelof et al., 1964) and others, isolated deficiency of IgG (Kadowaki et al., 1965) or deficiency of IgG and IgA and increase in IgM (Fireman, Johnson, and Gitlin, 1966). It is of interest that in our series, 6 of 7 patients in whom the γ-globulins were low (measured by either
technique) died within the first 9 months of life. In the other 5 cases, death occurred between 10 months and 5 years. There appears to be a correlation between longevity and the \( \gamma \)-globulin production.

In 4 patients the iso-agglutinins were looked for, and were not found in Cases 2 and 10, one of which closely resembled the Aldrich syndrome. In Case 2 where the IgM was measured, a low value was obtained. The presence or absence of iso-agglutinins is a simple laboratory test which may be of some diagnostic value. These substances were not present in the XX/XY chimera with thymic aplasia described by Kadowaki et al. (1965), and are known to be absent in the Aldrich syndrome (Cooper et al., cited by Chilgren et al., 1967), a further point of interest with regard to Case 10.

At this stage of knowledge of the pathogenesis of the disease, further classification into different variants of this syndrome is unhelpful, but the association of glomerulonephritis with one of our cases and its presence in the case of Schaller et al. (1966), suggests that a wide range of disease of altered ‘self-recognition’ may be described in this type of patient. Possibly the haemolytic anaemia with haemophagocytosis is a further example of this.

The results of simple quantitation of lymphocytes and immune globulin levels will not necessarily support or refute a clinical impression of an immune deficiency state. Lymph node biopsy, splenic biopsy, or the assessment of the state of development of the gut-associated lymphoid tissue (tonsillotemy, appendicectomy, colonic biopsy) may not provide histological evidence of abnormality. Functional tests of lymphocyte activity and cellular immunity are thus necessary for diagnosis, and also provide additional methods for the study of the pathogenesis of this type of illness.

The true incidence of these illnesses is unknown but it is probably more common than the number of reported cases suggests. Most of our patients were undiagnosed in life and found only by reviewing the thymic histology of a large series. They are, of course, a selected group in so much as the majority had been referred to this hospital originally from other centres, often as ‘failure to thrive’. Nevertheless, an incidence from these figures of 17 of 1000 necropsied child cases is surprisingly high.

**Summary**

A clinico-pathological study of 17 patients with thymic abnormality and associated changes in other lymphoid structures has been described; 14 patients had a strikingly similar clinical picture of failure to thrive, diarrhoea, and recurrent infection. Lymphopenia and hypo-\( \gamma \)-globulinemia were not invariant findings, and abnormalities in tissues other than the thymus were not constant. Other forms of investigation led to better definition of the immune defects present are discussed.

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**References**


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