Congenital Aplasia of Parathyroid Glands and Thymus

J. HUBER, P. CHOLNOKY*, and H. E. ZOETHOUT

From the Departments of Pathology and Paediatrics, State University, Groningen, The Netherlands

Congenital absence of the parathyroid glands may be associated with congenital absence of the thymus (Lobdell, 1959). This is not surprising as both structures arise together from the 3rd and 4th branchial pouches. In the same way, vascular anomalies of the 3rd and 4th branchial arteries are found to be associated with abnormalities of the thymus, including thymic aplasia (Cameron, 1965).

A patient is described in whom thymic aplasia, absence of the parathyroid glands, and congenital heart disease were present. The interest of this case lies in the light this 'experiment of nature' may shed on the immunological systems of the body.

Case Report

A male child of 4100 g., delivered by caesarean section after normal pregnancy, was admitted a few hours after birth because of persistent severe cyanosis present from birth. Clinical, ECG, and radiological findings suggested a diagnosis of severe pulmonary stenosis, possibly pulmonary atresia, and this was confirmed at the age of 3 months by angiocardiology, when the findings were consistent with Fallot's tetralogy with severe infundibular pulmonary stenosis. From the first day of life he had convulsions, which correlated with low serum calcium levels. Treatment with oral and intravenous calcium only partially and temporarily raised the serum calcium level sufficiently to stop the convulsions. Administration of parathormone, however, immediately stopped the convulsions, and resulted in normal or high serum calcium concentrations (Table). Parathormone also increased calcium and phosphate excretion in the urine.

The infant was put on permanent parathormone treatment, in varying dosage according to blood calcium determinations. After four weeks, the serum calcium level could no longer be maintained by parathormone treatment, and instead high doses of vitamin D (20,000–50,000 units per day) were given, resulting in a fairly consistently normal blood calcium level.

At the age of 6 months, the weight being 4850 g., there was a short episode of haematuria lasting one day, and a few days later he died in heart failure and severe anoxia.

At no time had there been any gastro-intestinal disturbance.

Laboratory data. Hb 14–15 g./100 ml., haematocrit 50–55%; WBC 10,000–12,000/c.mm., lymphocytes 20–50%. Blood group O Rh positive. Serum protein 5.5 g./100 ml. (albumin 52.2%, α_1 -globulin 5.8%, α_2 -globulin 15.4%, β -globulin 15.5%, γ -globulin 11.1%). PBI 6.5 μ g./100 ml. at the age of 6 weeks, before angiocardiology. X-ray film of the knee at the age of 2 months showed distal femoral and proximal tibial ossification centres to be normal.

Chest x-ray films between birth and 6 months showed normal heart size; decreased pulmonary vasculature; no evidence of a thymic shadow; and prominent right atrium.

X-ray film of the abdomen at age 4 months showed no calcium deposits.

Necropsy was performed six hours after death. There was brachycephaly, flat bridge to nose, and a large tongue.

Heart: weight 75 g.; right atrium and right ventricle were distended. There was a small crescent-shaped fossa ovalis defect, large ventricular septal defect, and infundibular and valvular pulmonary stenosis. The right ventricular wall was hypertrophied. The ductus arteriosus was closed. Normal vessels were arising from the aorta.

Tonsils were present; the thymus was absent. Parathyroid glands were absent on inspection. The absence of both thymus and parathyroid tissue was confirmed by examining all mediastinal and neck tissue in 5 mm. slices which were serially sectioned in 10 μ sections at 100 μ intervals.

TABLE
Effect of Treatment on Serum Calcium and Phosphorus Levels

Treatment	Serum Calcium (mg./100 ml.)	Serum Phosphorus (mg./100 ml.)
None	7.5, 6.1	5.6
Vitamin D (3000 u./day)	6.4	—
Parathormone	10.0	6.3
Vitamin D (30,000 u./day)	10.4	4.7
Vitamin D (25,000 u./day)	8.4	5.6

Received August 8, 1966.

* Present address: Department of Paediatrics, University of Pécs, Hungary.

FIG. 1.—Lymph node, showing well-developed germinal centres. (H. and E. $\times 60$.)

FIG. 2.—Lymph node, showing germinal centres with plasma cells. (Methyl green-pyronin. $\times 590$.)

The thyroid gland was normal with normal histology. *Lungs*: petechial haemorrhages; food aspiration; microscopic calcium deposits in the septa. *Liver*: gross engorgement. *Kidneys*: microscopic calcium deposits.

Lymph node system present. In the nodes, there were normal germinal centres (Fig. 1) and normal plasmacellular reactivity (Fig. 2). In the spleen, germinal follicles were observed in the neighbourhood of arterioles without a lymphocyte cuff (Fig. 3).

Intestine: Peyer patches present. Brain was not examined.

Discussion

Although there were clinical signs of congenital heart lesion and of disturbed calcium metabolism during life, no signs were noted to suggest immunological incompetence, despite thymic aplasia.

Miller (1965) discussed the role of the thymus in immune processes. The effect of thymectomy on the development of the lymphoid system and on the immunological capacity depends on the stage of growth of the peripheral lymphoid structures at the time of thymectomy in a given animal species. Experimental destruction of the thymic tissue in chickens by surgery, irradiation, or chemical means (Glick, Chang, and Jaap, 1956) has shown that in

this animal another organ plays an important role in the development of the peripheral lymphoid system. This is the bursa of Fabricius, localized at the cloacal region. Cooper, Peterson, and Good (1965) have assigned a different specific function to the thymus and bursa, respectively. The thymus is possibly responsible for cellular immunity, the bursa being its counterpart as regards humoral immunity. Bursectomy at an early stage of development leads to hypo- γ -globulinaemia, while cellular immunity remains normal. Thymectomy mainly affects cellular immunity.

An equivalent human structure to the avian bursa has not yet been designated, though it has been suggested that the lympho-epithelial tissue along the gut may have the same functional importance as the bursa. In the 'Swiss type' of hypo- γ -globulinaemia (Hitzig and Willi, 1961), there is a combined cellular and humoral immunological incompetence.

This infant had shown no signs of immunological incompetence, infections playing no role in the clinical picture. Normal values were found for serum γ -globulin at the age of 6 weeks, though this may have been partly of maternal origin.

FIG. 3.—Spleen. Germinal follicle in the neighbourhood of an arteriole lacking any cuff of lymphocytes. (Methyl green-pyronin $\times 160$.)

It is noteworthy that the peripheral lymphoid system, i.e. tonsils, nodes, and intestinal tissue, was present, though small lymphocytes were scarce. This may mean that the 'bursa-dependent' cortical areas with normal germinal centres and plasma-cellular reaction were present, while the 'thymus-dependent' areas showed lympho-depletion. There was no blood lymphopenia, or symptoms of runting.

DiGeorge (1965) mentions a patient with congenital hypoparathyroidism and absence of the thymus. This patient had normal humoral immunity but deficient cellular immunity, as he failed to reject a skin homograft three months after the graft had been performed. He did not have lymphopenia but showed severe runting, in which aspect he differs from our patient. The findings in these cases suggest that without a thymus the peripheral lymphoid 'bursa-dependent' follicular system develops normally. This fact lends support to the theory (Peterson, Cooper, and Good, 1965) that there are two immunological systems, each controlled by a different organ, one of which is the thymus.

Summary

An infant is described, with congenital absence of thymus and parathyroids. Death occurred at 6 months from heart failure due to a severe congenital heart lesion. At no time were any signs of immunological incompetence observed. The theoretical implications of this are discussed.

REFERENCES

- Cameron, A. H. (1965). Malformations of the thymus and cardiovascular system. In Paediatric Pathology Club, Proceedings of the tenth annual meeting. *Arch. Dis. Childh.*, **40**, 334.
- Cooper, M. D., Peterson, R. D. A., and Good, R. A. (1965). Delineation of the thymic and bursal lymphoid systems in the chicken. *Nature (Lond.)*, **205**, 143.
- DiGeorge, A. M. (1965). Discussions on a new concept of cellular basis of immunity. *J. Pediat.*, **67**, 907.
- Glick, B., Chang, T. S., and Jaap, R. G. (1956). The bursa of Fabricius and antibody production. *Poult. Sci.*, **35**, 224.
- Hitzig, W. H., and Willi, H. (1961). Hereditäre lympho-plasmocytäre Dysgenese. *Schweiz. med. Wschr.*, **91**, 1625.
- Lobdell, D. H. (1959). Congenital absence of the parathyroid glands. *Arch. Path.*, **67**, 412.
- Miller, J. F. A. P. (1965). The role of the thymus in immune processes. *Int. Arch. Allergy*, **28**, 61.
- Peterson, R. D. A., Cooper, M. D., and Good, R. A. (1965). The pathogenesis of immunologic deficiency diseases. *Amer. J. Med.*, **38**, 579.