Z Rechtsmed (1987) 98:119–123

Zeitschrift für
Rechtsmedizin

Kasuistiken / Casuistics

Immunologic Defects as Possible Causes of Therapeutic Failures in Children with Transposition of the Great Arteries*

T. Marek-Szydłowska[1], L. Szydłowski[2], W. Uracz[3], and M. Zembala[3]

[1]Mother and Child Center, [2]Department of Cardiology and [3]Department of Clinical Immunology, Institute of Pediatrics, Medical Academy, Wielicka 265, PL-30-663 Cracow, Poland

Summary. Recurrent and severe infections and absence of thymic shadow in X-ray examination were observed in children with the transposition of the great arteries (TGA). Among 45 children (29 boys and 16 girls) with TGA whose age ranged from 3 days to 16 years and who were hospitalized during 1 year, infectious diarrhea was observed in 77.7% cases, urinary tract infections in 44.5%, respiratory tract infections in 42.2%, sepsis in 17.5%, and meningitis in 8.8%. Nine of the children died, sepsis was a cause of death in seven children, and there were postsurgical complications in two children. Immunologic abnormalities in children with TGA included a decreased level of T-lymphocytes and $T_{29^{\circ}}$ subpopulation, impaired mitogen-induced lymphoproliferation in vitro, and increased nitro blue tetrazolium (NBT) reduction activity of monocytes. Impaired parameters of cellular immunity correlated with worst clinical status. No disorders of humoral immunity were observed. These observations may be important for forming opinion about proper therapy and the cause of death in children with TGA.

Key words: Transposition of the great artries – Immunologic abnormalities, opinioning of the cause of death

Zusammenfassung. Bei Kindern mit angeborener Verlagerung der großen Arterien wurden schwere, häufig wiederkehrende Infektionen ohne Auftreten eines Thymus-Schattens im Röntgenbild beobachtet. Bei 45 Kindern (29 Knaben, 16 Mädchen) im Alter von 3 Tagen bis 16 Jahren, die wegen dieser Anomalie für 1 Jahr hospitalisiert waren, traten in 77,7% der Fälle infektiöse Durchfälle, in 44,5% Harnwegsinfektionen, in 17,5% Sepsis und in 8,8% der Fälle Meningitis auf. Neun der Kinder starben, wobei in sieben

Offprint requests to: T. Marek-Szydłowska (address see above)

* All results have been included in T. Marek-Szydłowska's doctoral dissertation and were communicated at the 65th Annual Meeting of Deutsche Gesellschaft für Rechtsmedizin, St. Gallen, Switzerland, Sept. 9–13, 1986

Fällen Sepsis und in zwei Fällen postoperative Komplikationen Todesursachen waren. Immunologische Veränderungen ließen sich bei den Kindern anhand einer gesteigerten T-Lymphozyten- und T-29°-Unterpopulations-Zahl, in der gestörten Mitogen-induzierten Lymphozytenproliferation in vitro und einer vermehrten Nitroblau-Tetrazolium (NTB)-Reduktions-Aktivität der Monozyten nachweisen. Es wurden jedoch keine Beeinträchtigungen in der humoralen Immunität beobachtet. Die Befunde können für die Beurteilung einer geeigneten Therapie und der Todesursache bei Kindern mit Arterienverlagerungen von Bedeutung sein.

Schlüsselwörter: Transposition der großen Gefäße, Infektionen – Immunologischer Defekt, Todesursache bei Transposition der großen Gefäße

Introduction

Due to the development of cardiology and cardiosurgery prognosis in congenital heart diseases, such as transposition of the great arteries (TGA) in newborns improved considerably within the past few years. Till recently, it was considered lethal (Paul 1983; Lambert et al. 1966). At present, there are two steps of therapy. The first is to perform atrial balloon septostomy modo Rashkind during the first days of the child's life which is considered critical for successful therapy. The second step is a radical surgical correction of TGA (Coto et al. 1979).

The continuously growing number of recovered children makes us believe that TGA treatment should be successful in all cases (Levy et al. 1978). That is why parents often consider therapeutic failure a malpractice and often accuse physicians of having committed it. Sudden deterioration of the clinical condition of children who underwent successful cardiologic and cardiosurgical treatment often surprises not only parents but physicians, too. The main complications are serious and recurrent infections of digestive, respiratory, nervous, and urinary systems as well as sepsis (Waldman et al. 1977). Most of these infections are refractory to standard treatment and it is often difficult to establish the cause of unexpected death. In fact, in such cases it might be difficult for experts to pass a medico-legal opinion on the cause of death. The verdict may also be an undeserved charge for a physician.

The present studies were designed to establish the underlying cause of sudden and serious infections and a poor prognosis in children with TGA. As it is known that some immunologic disorders are associated with congenital heart diseases and a lack of thymic shadow on X-ray examination (Asherson and Webster 1980; Bockman and Kirby 1984; Duncan et al. 1984), clinical and immunologic examinations were undertaken in this group of children.

Material and Methods

Patients, 45 children (29 boys and 16 girls) with TGA ranging in age from 3 days to 16 years were hospitalized for 1 year (1985) in the Dept. of Cardiology. The

diagnosis was based on clinical examination confirmed by heart echocardiography. Careful clinical, microbiologic, and immunologic examinations were performed in each case. Two control groups were established: sex- and age-matched children without any congenital heart disease and with other cyanotic congenital heart diseases.

Results

Among 45 children with TGA infections diarrhea was observed in 77.7% cases, urinary tract infections in 44.5%, respiratory tract infections in 42.2%, sepsis in 17.5% and meningitis in 8.8% (Fig. 1). The most common causes of infections were candidiasis (35.5%) and pneumocytosis (17.5%). Nine of the children died: sepsis was a cause of death in seven children and postsurgical complications in another two children (Fig. 2).

The constant finding was the absence of the thymic shadow in X-ray chest examination in all children.

Immunologic abnormalities in children with TGA included a decreased level of T-lymphocytes and their $T_{29^{\circ}}$ subpopulation bearing high affinity receptors for sheep red blood cells. The impaired mitogen-induced lymphoproliferation in vitro was also observed. This was often accompanied by an increased NBT

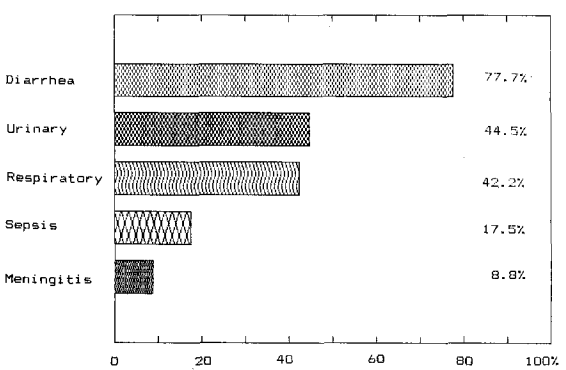

Fig. 1. Frequency of infections

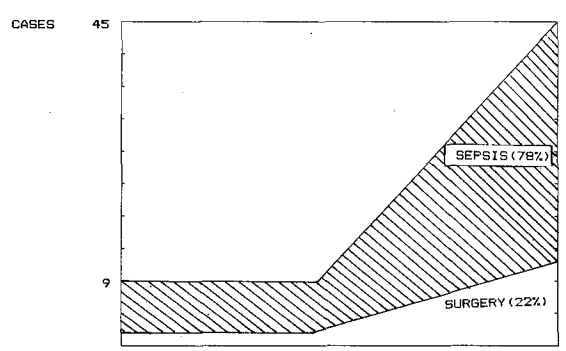

Fig. 2. Causes of death

reduction activity of monocytes. No disorders of humoral immunity were observed as serum immunoglobulin levels were within normal range.

The two typical examples illustrating an unfavorable clinical course of children who had undergone successful cardiologic and cardiosurgical treatment are given.

Case 1

B.M., male, birth 3460 g, uncomplicated full-term pregnancy and delivery. Both parents were young and healthy and of good social status. At 24 h after birth TGA was diagnosed. Two days later, the child underwent catheterization of the heart for the palliative procedure (balloon septostomy). X-ray chest examination showed typical configuration of the heart and absence of the thymic shadow. The infant was hospitalized four times within 6 months. Recurrent and severe infections of digestive and respiratory tracts were the reason for hospitalization. Candidiasis, pneumocytosis, and sepsis (Streptococcus) were diagnosed during the last admission. Despite of intensive treatment the child died. Congenital heart disease (TGA) and very dilatated "foramen ovale" after Rashkind procedure (11 × 19 mm), leptomeningitis purulenta and generalized sepsis were found on the post-mortem examination.

Case 2

J.J., female, birth weight 3870 g, full-term pregnancy and a normal delivery. She was the first baby born to a 28-year-old mother from the well-off family. Transposition of the great arteries was diagnosed on day 2 of life, and Rashkind's procedure was performed on day 11 of life. X-ray chest examination showed typical configuration of the heart and no thymic shadow. During the next few days she developed diarrhea and Pheumocystis pneumonia, both of which were successfully treated. The neonatal period was normal. Up to 7 months of age she was described as normally developed infant. However, she had frequent and recurrent infections of digestive and respiratory tracts. At the age of month 7 the girl was admitted to hospital because of sepsis. Staphylococcus aureus was isolated from the blood. During hospitalization she also developed diarrhea, pneumocystosis, bronchitis, and otitis media. She responded to prolonged treatment with antibiotics and Lomidine supplemented with Sandoglobulin. Sepsis was complicated by right hemiparesis. Computer tomography (CT) revealed cerebral atrophy. At the age of 10 months radical correction modo Senning was performed. At present, she is a 16-month-old girl, fairly compensated by requires frequent hospitalization because of severe recurrent infections.

Discussion

These studies were designed to determine the factors responsible for the recurrent infections complicating the clinical course of transposition of great arteries (TGA) in children. Chronic infections were resistant to standard treatment and often were the cause of therapeutic failure and death despite the proper cardiologic and cardiosurgical approach. In fact, among nine children who died, sepsis was a cause of death in seven children and postsurgical complications only in two children. The absence of thymic shadow in X-ray chest examination was the consistent finding. The most common infections were candidiasis and pneumocystosis. Immunologic abnormalities in children with TGA included a decreased level of T-lymphocytes and $T_{29^{\circ}}$ subpopulation. In parallel, impaired mitogen-induced lymphoproliferation in vitro was observed

which suggested the depression of cell-mediated immunity. This was often accompanied by an increased NBT reduction activity of monocytes. The increased NBT reduction activity might indicate the non-specific activation of cells of monocyte/macrophage lineage due to infection. No disorders of humoral immunity were observed as serum immunoglobulin levels were within normal range. Impaired parameters of cellular immunity and absence of the thymic shadow correlated with the worst clinical status.

These results suggest that impairment of cellular immunity and not the inappropriate management or false therapy of children with TGA might be responsible for the occurrence of severe infections which are the immediate cause of death. These factors may be important for forming a medico-legal opinion on the cause of death.

References

Asherson GL, Webster ADB (1980) Diagnosis and treatment of immunodeficiency diseases. Blackwell, Oxford London Edinburgh Melbourne

Bockman De, Kirby ML (1984) Dependence of thymus development on derivates of the neutral crest. Science 223:498–500

Coto EO, Norwood WI (1979) Modified Senning operation for treatment of transposition of the great arteries. J Thorac Cardiovasc Surg 78:721–729

Duncan WI, Tyrrell MI, Bharadwaj B, Rosenberg AM, Schroeder ML, Bingham WT (1984) Complex transposition with interrupted right aortic arch and partial di George syndrome: successful palliation with combined medical and surgical therapy. Pediatr Cardiol 5:217–220

Lambert EC, Canent RV, Hohn AR (1966) Congenital cardiac anomalies in the newborn. A review of conditions causing death or severe distress in the first month of life. Pediatrics 37:343–351

Levy RJ, Rosenthal A, Castaneda AL, Nadas AS (1978) Growth after surgical repair of simple d-transposition of the great arteries. Ann Thorac Surg 25:225–230

Paul MH (1983) Transposition of the great arteries: In: Adams FH, Emmanouilides GC (eds) Moss' heart disease in infants, children and adolescents, 3rd edn. Williams & Wilkins, Baltimore London, pp 296–333

Waldman JD, Rosenthal A, Smith AL, Shurin S, Nadas AS (1977) Sepsis and congenital asplenia. J Pediatr 90:555–559

Received October 4, 1986