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Unexpected outcome (positive or negative) including adverse drug reactions

Arrival and survival of a 3-week-old boy from Pakistan with an arterial oxygen saturation of 17%

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SUMMARY

In newborn infants, acute perinatal hypoxic/ischaemic events and associated hyperoxia/reperfusion injury frequently lead to devastating neonatal brain damage. The present report concerns a 3-week-old boy from Pakistan with d-transposition of the great arteries (d-TGA), prolonged and severe hypoxaemia, and multiresistant bacterial sepsis. The term newborn infant underwent public airline transportation to Europe and presented on the airport's runway with severe hypoxaemia (pulsoximetric oxygen saturations (SpO2) 17%) and systemic hypotension. The patient eventually underwent late balloon atrial septostomy, followed by a successful two-stage arterial switch operation. A clinical follow-up 3–5 years later revealed lack of cerebral dysfunction, adequate neurodevelopment, good biventricular function, regular coronary flow, as well as normal ECG, blood pressure and SpO_2. The findings may indicate the neonatal brain adjusts better to chronic, slowly worsening hypoxia than to acute hypoxia (eg, "birth asphyxia"), and also suggests a greater tolerance for chronic hypoxia in neonates vs adults.

BACKGROUND

d-Transposition of the great arteries (d-TGA) is the most common cyanotic congenital heart defect to present in the first week of life,[1] affects 2.4 per 10 000 births,[2] and goes along with progressive moderate to severe postnatal hypoxaemia (pulsoximetric oxygen saturations (SpO2), approximately 40% to 85%). Apart from a small subgroup of infants that are severely depressed or even die immediately after birth, presumably due to early and rapid perinatal closure of foramen ovale and ductus arteriosus,[3,4] most patients with d-TGA/intact ventricular septum (iVS) are now successfully treated with prostaglandin E infusion, balloon atrial septostomy (BAS; Rashkind procedure)[5] and arterial switch operation in the first week of life.[6] Several investigators have found an association between early BAS[7] and one-stage arterial switch operation (reviewed in Cohen and Wernovsky)[6] on the one hand, and postinterventional stroke/brain damage[7] as well as mid-term to long-term neurological impairment of patients with d-TGA[6] on the other. Here, we report on a 3-week-old term infant with d-TGA/iVS, who had chronic, slowly worsening and finally severe hypoxaemia, underwent late BAS and two-stage arterial switch operation, but did not suffer from brain damage associated with significant neurodevelopmental delay at preschool age.

CASE PRESENTATION

Postnatal presentation

In May 2002, a 3-week-old boy from Pakistan with postnatally diagnosed cyanotic congenital heart disease arrived at the airport in Munich, Germany. Pregnancy was uneventful, followed by a normal vortex term delivery of the mother's fourth child in a private clinic in Pakistan (birth weight 3400 g). The baby cried normally after birth and Apgar scores were 5 at 1 min and 10 at 10 min. On day 2 of life, doctors noticed tachypnoea and central cyanosis. A provisional diagnosis of bronchopneumonia was made and the baby was transferred to the Children's Hospital neonatal intensive care unit (NICU). The baby remained in the NICU and was treated with intravenous antibiotics (cefotaxime, amikacin) although bacterial cultures remained negative. It was not until day 10 of life that persistent cyanosis was investigated further (fig 1A) and a paediatric cardiologist was asked to review the patient and perform an echocardiogram that showed d-TGA/iVS and a restrictive patent foramen ovale (PFO) (ie, 3 mm in diameter with an estimated interatrial pressure gradient (left atrial pressure>right atrial pressure) of 6 mmHg). Postductal SpO_2 at that time was 70% to 72%. Given the urgent need for cardiovascular surgery, the parents finally (10 days later) managed to schedule public airline transport to Munich. On the day of departure (day 19 of life, approximately 20 h before the patient's arrival in Munich) vital signs indicated progression of hypoxaemia (heart rate 130 beats/min, 45 breaths/min, postductal SpO_2 62%).

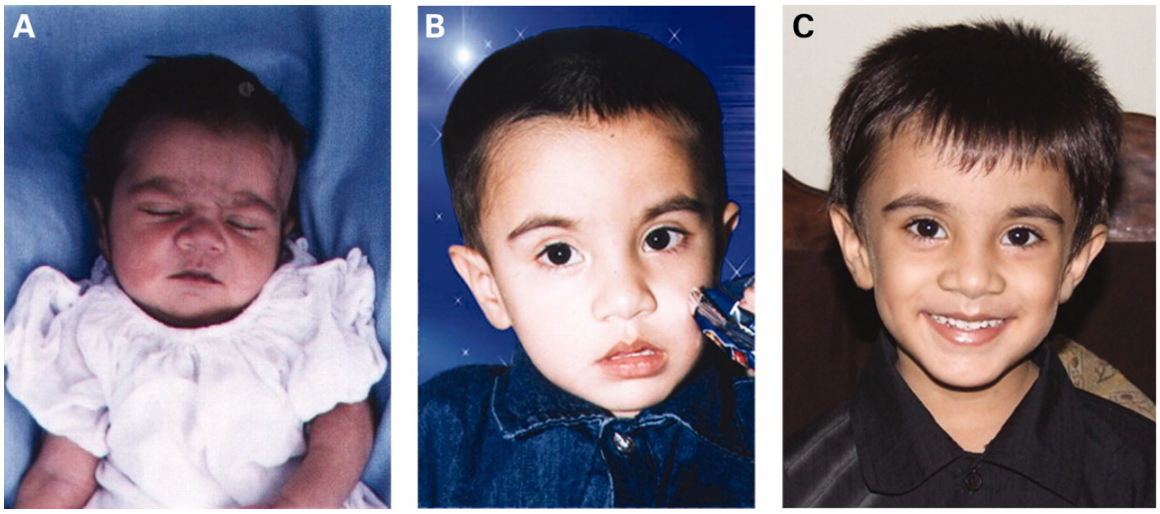

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Figure 1 A. Term infant (10 days old) born in Pakistan with central cyanosis and postductal pulsoximetric oxygen saturation (SpO_2) of 70% to 72% at day of diagnosis. For echocardiographic findings and cardiovascular diagnosis see text and fig 2. B,C. The same patient 3 years later (B) and 4 years later (C) in excellent clinical condition with SpO_2 of 98%, mild remaining right pulmonary artery stenosis, good cardiac function, normal ECG and adequate neurodevelopment.

Neonatal emergency transport and critical care

On the runway, the parents handed the neonatal transport team a pale, reasonably warm, shallow but regularly breathing boy (50 breaths/min) with central cyanosis and moderate dehydration. On auscultation, the heart rate (HR) was regular at 140–150 beats/min, first and second heart sounds were gentle and no murmur was heard. Initially, no pulse or blood pressure was obtainable. The liver was palpable 3.5 cm below the costal margin. Two separate pulsoximeters showed an arterial oxygen saturation (SpO_2) of 17% with good pulsoximetric waveform at the upper and lower extremities. The transport team had been told that the boy had d-TGA, had undergone BAS (Rashkind procedure) in Pakistan, and—for the duration of the flight—had had the attendance of an anaesthesiologist, prostaglandin E infusion and supplemental oxygen if needed.

On arrival, however, the infant had not been seen by any doctor for at least 12 h. Based on the patient's compromised clinical condition, the emergency paediatrician assumed the initial diagnosis was correct, but that the atrial and ventricular septum were both intact and the foramen ovale and ductus arteriosus had closed (ie, no shunt). With supplemental oxygen (100%, 10 l/min) SpO_2 rose to 40%. Two peripheral venous lines were placed. Volume substitution (normal saline) and high-dose prostaglandin E (PGE) infusion (100 ng/kg per min intravenously) were started. The baby continued to breathe spontaneously, a pulse became detectable (130–145 beats/min), and mean arterial blood pressure (MAP) and SpO_2 were recorded to be 55 mmHg and 40% to 50%, respectively.

The infant arrived on the cardiovascular intensive care unit (CVICU) at 18:30 h, after 40 min of ground-based transport and additional low-dose sodium bicarbonate infusion (0.7 mEq/kg/dose=1 mEq/kg/h while on transport), with HR 155 beats/min, MAP 38 mmHg and SpO_2 42% to 55%. After analgosedation, muscle relaxation, endotracheal intubation and positive pressure ventilation with 100% oxygen, SpO_2 initially dropped to 29% but increased to 39% over the next 20 min. Arterial blood gas analysis (18:56 h) immediately after intubation showed severe hypoxaemia (partial pressure of oxygen in arterial blood (PaO_2) 13 mmHg) but no acidosis (pH 7.47, $PaCO_2$ 36 mmHg, base excess +2 mmol/litre, lactate 3.2 mmol/litre). Volume replacement was continued via a central venous line, however the baby remained borderline hypotensive and severely hypoxaemic so that moderate dopamine (8 µg/kg/min) and norepinephrine (0.07 µg/kg/min) infusions were initiated. The initial echocardiogram demonstrated d-TGA with iVS, minimal shunts across the atrial septum and the ductus arteriosus, and impaired biventricular function. An echocardiographically-guided balloon atrial septostomy (BAS, Rashkind procedure;[5] fig 2) was performed 90 min after the patient's arrival on the CVICU, leading to a rapid increase of SpO_2>60%, followed by a continuous rise of SpO_2 up to 76% over the next 90 min, and discontinuation of PGE infusion.

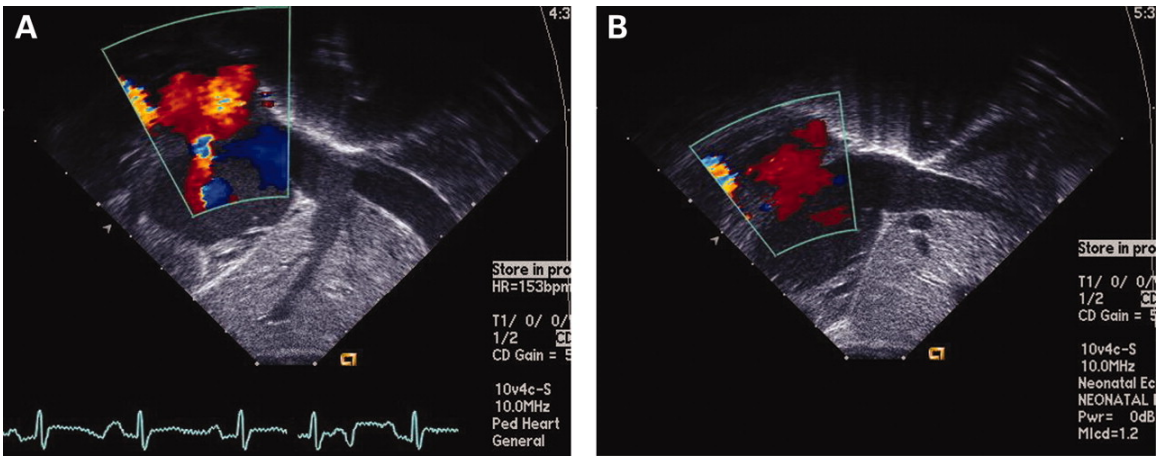

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Figure 2 Colour Doppler echocardiography showing left-to-right atrial shunting via a patent formamen ovale (PFO) in a newborn infant with d-transposition of the great arteries (d-TGA). A. Restricted interatrial blood flow from the left atrium (LA) through the PFO into the right atrium (RA) as indicated by the narrowing and turbulence of the red signal across the atrial septum. Systemic venous return via the inferior vena cava (IVC) into the RA is indicated by blue colour. B. Aimilar image as (A) after successful balloon atrial septostomy (BAS; Rashkind procedure). Note the large left-to-right atrial shunt after the successful procedure.

After stabilisation of the infant, comprehensive history taking revealed that d-TGA/iVS had been diagnosed late on day 10 of life in Pakistan, where usual counselling would have been "terminal care". The parents decided to ask for international help and requested urgent BAS as well as international neonatal emergency transport. However, the only capable cardiologist in 300 km radius had a hand injury on the day of the

scheduled procedure so that a BAS, in fact, was not performed in Pakistan. On their own initiative, the parents subsequently scheduled public airline transport during which they noticed their baby getting even more blue.

Cardiovascular surgery

The biventricular dysfunction in this severely compromised patient rendered the decision for a rapid two-stage arterial switch operation: 2 days after arrival and BAS, a central aortopulmonary shunt (3.5 mm), atrioseptectomy and pulmonary arterial banding were performed to improve systemic oxygenation and to train the left ventricle in anticipation of the arterial switch operation. Postoperatively, multiresistant bacterial sepsis (acquired in Pakistan) was successfully treated with intravenous antibiotics, and cardiac function improved. At 9 days after the first operation, an uncomplicated arterial switch operation was performed on the then almost 5-week-old infant. The boy was discharged 1 month later in excellent haemodynamic and neurological condition, with SpO_2 of 95%, a remaining pressure gradient (dP) over the pulmonary artery (PA; dP 55 mmHg at the PA bifurcation on Doppler echocardiography), and normal head ultrasound.

OUTCOME AND FOLLOW-UP

Clinical follow-up

At follow-up 3, 4 and 5 years later, the patient was found to be an active, healthy boy (fig 1B,C). Cardiac follow-up showed good biventricular function, regular coronary flow, improved right PA stenosis (dP 30 mmHg by Doppler echocardiography), and normal ECG, blood pressure and SpO_2 (98%). The developmental milestones were assessed on Schedule of Growing Skills (SGS-II)[8] and demonstrated adequate neurodevelopment at 5 years of age (table 1). The child currently is 6 years old, in first grade of a regular school and doing well in academics according to school report.

Table 1 Schedule of Growing Skills (SGS-II) of the patient at 5 years of age

Skill level	Age level (developmental index)
Locomotor	60 months (100%)
Manipulative	48 months (80%)
Visual	60 months (100%)
Hearing and language	60 months (100%)
Speech and language	60 months (100%)
Interactive social	60 months (100%)
Self-care social	50 months (83%)
Cognitive	50 months (83%)

The developmental index (ie, (developmental age level/chronological age)x100) is given in parentheses. A developmental index ≥ 80% indicates adequate neurodevelopment.

Table 1 Schedule of Growing Skills (SGS-II) of the patient at 5 years of age

DISCUSSION

Acute perinatal hypoxic/ischaemic events and associated hyperoxia/reperfusion injury ("birth asphyxia")[9–12] frequently lead to devastating neonatal brain damage,[13] and strategies how to treat acute perinatal hypoxia are subject of an ongoing debate.[12,14–17] Our description of a newborn infant with d-TGA surviving chronic, slowly progressing, and finally severe hypoxaemia, ballon atrial septostomy[7] and late arterial switch operation[6] without any cerebral dysfunction or significant neurodevelopmental delay is quite remarkable.

Our newborn patient clearly adapted to chronic, slowly worsening hypoxia, and survived the period of most severe hypoxia (SpO_2 17%, PaO_2 13 mmHg), catheter intervention and cardiovascular surgery without significant morbidity. Postductal SpO_2 was 70% to 72% on day of life 10. The worsened postductal SpO_2 of 62% on the day of departure (day of life 19, in Pakistan, approximately 20 h before arrival) is in line with the natural course of untreated d-TGA (ie, closing of patent ductus arteriosus (PDA) and PFO, usually in the first 2 weeks of life). Then, during the intercontinental flight, the flow restriction through the PFO may have worsened or stayed the same, but the small ductus arteriosus (that might have been marginally open before departure) functionally closed (no PGE intravenous infusion). Accordingly, the parents noticed their son getting very blue while still in the aircraft cabin, and the boy would have almost certainly died within the next few hours if not treated. On arrival in Munich, the left atrial to right atrial shunt and systemic oxygenation increased with the administration of intravenous volume and high dose PGE infusion. We might have reopened the ductus arteriosus to some extent, however, given the echocardiographic study performed in the CVICU in Munich, the ductal shunt prior to the Rashkind procedure was nevertheless very small. The rapid balloon atrial septostomy dramatically improved all the shunt on the atrial level, systemic oxygenation and haemodynamics, so that subsequently the patient was stable enough to undergo a two-stage arterial switch operation.

The PaO_2 at which 50% of haemoglobin is saturated (P50) averages 22 mmHg in the newborn.[18] Given the sigmoid shape of the oxygen/haemoglobin dissociation curve, lack of severe acidosis and reliable pulsoximetric waveform, it can be realistically estimated that the patient's PaO_2 in room air on arrival at the airport was approximately 10–16 mmHg (when SpO_2 was 17%). We are not aware of any other published case report, describing an older child or adult surviving several days with arterial oxygen saturations persistently below 65%, followed by a period several hours long where SpO_2 was below 20%. This report therefore may suggest a greater tolerance for chronic hypoxia in neonates vs adults.

Moreover, the patient's clinical course and follow-up may indicate the neonatal brain adjusting better to chronic, slowly worsening hypoxia than to acute hypoxia[13] (eg, in birth asphyxia). Whether this is due to decreased cerebral energy metabolism and/or increased cell survival and resistance to apoptosis in the context of chronic (rather than acute) hypoxia is unknown. Ischaemic preconditioning (ischaemic tolerance)[19] is the process by which a subthreshold ischaemic insult applied to the brain activates certain genes sets and cellular pathways that can reduce damage caused by subsequent ischaemic episodes. In fact, cerebral ischaemic preconditioning in animal models of stroke provided solid neuroprotection against subsequent

ischaemic injury,[20] and previous transient ischaemic attacks were associated with better clinical outcome after subsequent stroke in humans.[21] Researchers have just begun to unravel the underlying molecular processes; in a mouse model of cerebral ischaemia, preconditioning resulted in transcriptional changes involved in the suppression of metabolic pathways and immune responses, reduction of ion channel activity and decreased blood coagulation.[22] Downregulated genes were those that control metabolism, cell cycle regulation and ion channel activity. These features mimic specific adaptive neuroprotective strategies seen in hypoxia-tolerant states such as hibernation (which occurs, for example, with therapeutic hypothermia[17,23]). It is possible that the chronic, slowly worsening hypoxia and haemodynamics in our patient preconditioned the neonatal brain[23] to the severe hypoxia/ischaemia at the time of critical shunt closure, and to the subsequent periods of cardiopulmonary bypass that is—despite all intraoperative efforts—frequently associated with variable degrees of cerebral hypoperfusion and hypoxia. Nevertheless, it should be underlined that children with congenital heart disease continue to have a high rate of cerebral injury on MRI (even abnormal brain development in utero)[24] and significant burden of neurodevelopmental disability when compared with their healthy peers.[6,25,26]

LEARNING POINTS

- This case report indicates the neonatal brain adjusting better to chronic, slowly worsening hypoxia than to acute hypoxia (eg, birth asphyxia in the delivery room).
- While there seems to be a subgroup of infants with d-transposition of the great arteries, intact ventricular septum (d-TGA/iVS) that are severely depressed or even die immediately after birth, presumably due to early and rapid perinatal closure of the foramen ovale and ductus arteriosus,[3,4] this case report suggests there might be another subgroup of patients with d-TGA/iVS who either resist or tolerate shunt reduction and associated progressing hypoxia for a longer period of time.
- Another learning point from this patient encounter is related to the management of neonates who are diagnosed late with d-TGA/iVS. Typically in patients with d-TGA/iVS and flow restrictive atrial septum, neither late attempts to reopen the ductus arteriosus with prostaglandin infusions, nor positive pressure ventilation with 100% oxygen are likely to markedly increase the amount of oxygenised blood in the aorta, as experienced in the case scenario described above.
- In adults, such prolonged and severe hypoxaemia, with partial pressure of oxygen in arterial blood (PaO_2)<20 mmHg for several hours, would have been incompatible with life. This report therefore also may suggest a greater tolerance for chronic hypoxia in neonates vs adults.
- Moreover, our report encourages international efforts to assist cardiovascular emergencies in developing countries, but also demonstrates that those transports can be unpredictable.

We would like to thank our colleagues, the international donors and organisations that made transport, cardiovascular surgery, critical care and follow-up possible, and the patient's parents for their consent to publish this case report. GH received support from the American Heart Association (AHA)/Pulmonary Hypertension Association (grant 0425943H) and the German Interdisciplinary Association of Critical Care Medicine (DIVI). GH is a member of the American Thoracic Society (ATS), the AHA Council on Cardiopulmonary, Perioperative and Critical Care and the European Resuscitation Council (ERC).

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Patient consent: Patient/guardian consent was obtained for publication.

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