well as galactitol concentrations in amniotic fluid about 15 times above normal have been well documented in early second trimester fetuses.⁴ To our knowledge, galactose and its metabolites have not been measured in gonadal tissue so far. A striking reduction in the number of small oocytes was found in the offspring of rats fed a 50% galactose diet in the first two thirds of pregnancy.⁵

Thus, prenatal exposure to galactose or its metabolites may be a cause of premature ovarian failure in human galactosaemia. Whether the toxic agent is of maternal or fetal origin remains to be established. There is good evidence that transferase deficient infants can synthesise galactose-1-phosphate from glucose via the epimerase and pyrophosphorylase pathway which may lead to self intoxication.⁶ Therefore, strict avoidance of galactose in some high risk pregnancies may not be sufficient for prevention of gonadal damage in the galactosaemic offspring. Familial expression of galactosaemia may differ as not all homozygous women have ovarian failure¹ and correlation between initiation of treatment and hypogonadism

may be poor,² (this report). Clearly more detailed and carefully planned studies are necessary to elucidate these new problems in this otherwise well known disease.

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Received 28 February 1984

Familial persistent pulmonary hypertension

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SUMMARY We report three siblings who presented with a clinical picture of persistent pulmonary hypertension of newborn and died between 4 and 15 days of age. Pulmonary artery pressure in all was above systemic values, with a right to left shunt via either the foramen ovale or ductus arteriosus, or both. Histology of the pulmonary vascular bed showed extension of muscle into small arteries which are normally non-muscular.

The term persistent pulmonary hypertension of newborn refers to a condition in which pulmonary artery hypertension prevents the successful transition from the fetal to adult circulation.¹ The neonate continues to have raised pulmonary vascular resistance, with pulmonary artery pressure higher than systemic values. Persistent right to left shunting through the foramen ovale and ductus arteriosus results in hypoxaemia, acidosis, and respiratory distress. Although most cases are associated with

well defined clinical entities,^{2,3} primary hypertrophy of the muscular layers of the pulmonary arterioles has been described.⁴

We report three siblings with persistent pulmonary hypertension of newborn associated with abnormal muscularisation of the intra-acinar pulmonary arteries. To our knowledge, this is the first report of familial primary pulmonary hypertension of the newborn, and the occurrence in three siblings suggests a recessively inherited genetic trait.

Case reports

Two boys and one girl from the same family with clinical and pathological features of persistent pulmonary hypertension of newborn are described. The infants were born to healthy parents of Tunisian origin who are first degree cousins. Two additional siblings born after the death of the first two sick infants are normal. No history of unexpected fetal or neonatal deaths in the extended family was recorded. The mother received no medication during

her pregnancies and had no known exposure to toxic agents.

All three infants were born after normal, term pregnancies and uneventful deliveries with no evidence of fetal distress. None had meconium staining of the amniotic fluid and one minute Apgar scores were eight or above in all infants.

Cyanosis and tachypnoea were the predominant presenting signs and were first noted at two, six, and one hour after birth respectively. All three infants had an accentuated second heart sound with narrow splitting. A blowing systolic murmur with no thrill was heard over the pulmonary area in one infant (case 1). Initial blood gases showed severe hypoxaemia and acidosis in all three infants (Table). A difference of greater than 20 mm Hg between radial and femoral arterial P_{aO_2} was found in two infants (cases 1 and 3). Blood biochemical and haematological studies were within normal limits. Blood, urine, and cerebrospinal fluid cultures were negative.

All infants had normal pulmonary parenchymal and vascular markings on chest radiographs with no cardiac enlargement. Electrocardiograms were within normal limits, showing no evidence of right ventricular strain or ischaemia. Echocardiographic examinations performed on two infants (cases 1 and 3) showed no structural cardiac abnormalities. Cardiac catheterisation showed that the pulmonary artery pressure was raised to suprasystemic values in all three infants (Table). A shunt at the level of the foramen ovale was found in all the infants and at the level of the ductus arteriosus in cases 1 and 3. No structural cardiac abnormalities were found.

Vigorous attempts to correct hypoxaemia and acidosis were unsuccessful in all infants. No response was obtained to intravenous tolazoline. Hyperventilation treatment adjusted to maintain

Figure Section of intra-acinar artery showing noticeable thickening of the vessel wall with the proliferation of smooth muscle cells in the media.

P_{aCO_2} at 20 to 25 mm Hg and pH above 7.5 failed to maintain the P_{aO_2} above 50 mm Hg in the third infant. One child died at age 4 days and the two others at the ages of 11 and 15 days.

A full necropsy was performed on all three infants. Cardiomegaly with mild dilatation of the right ventricle was found in all. In each, the foramen ovale was patent and in two (cases 1 and 3) the ductus arteriosus was patent. The lungs were inflated and fixed in 10% formalin. Thereafter, multiple random sections from each lobe were stained by haematoxylin-eosin, Masson's trichrome, toluidine blue, and elastin van Gieson. Morphological analysis of the pulmonary vascular bed was based on examination of the intra-acinar arteries measuring 100 to 150 μ m in the external diameter.⁵ The consistent prominent finding in all three infants was a noticeable thickening of the vessel wall accompanied by severe diminution of the size of the lumen (Figure). Special stains showed a striking proliferation of smooth muscle cells in the media of the intra-acinar arteries. The large muscular arteries and veins were normal. Arterioles in other organs were normal.

Discussion

Persistent pulmonary hypertension of the newborn occurs in a variety of clinical situations.¹⁻³ Intra-uterine hypoxia is probably the most important cause of hypertrophy of pulmonary vascular layers.⁶ Perinatal asphyxia is a common contributing factor to pulmonary vasoconstriction.^{2,7} Pulmonary hypoplasia, meconium aspiration syndrome, transient tachypnoea, group B streptococcal pneumonia, and hyaline membrane disease may be associated with this disorder.^{3,7} Less clearly defined are cases associated with a history of maternal ingestion of prostaglandin synthetase inhibitors.⁸ Idiopathic

Table Laboratory and special study results and response to treatment

	Case 1	Case 2	Case 3
Birthweight (kg)	3.3	3.8	3.6
Gestational age (weeks)	40	39	41
Cardiac catheterisation			
Aortic pressure (mm Hg)	62/50	71/40	55/30
Pulmonary artery pressure (mm Hg)	70/50	90/45	60/30
Patent foramen ovale	Yes	Yes	Yes
Patent ductus arteriosus	Yes	No	Yes
Before treatment			
pH	7.02	6.93	7.11
P_{aO_2} (mm Hg)	28	19	34
P_{aCO_2} (mm Hg)	47	53	44
Hyperoxia test (F_{iO_2} 1.0)			
P_{aO_2} (mm Hg)	43	30	50
Response to tolazoline			
P_{aO_2} before (mm Hg)	34	25	48
P_{aO_2} after (mm Hg)	41	26	52

primary hypertrophy of the muscular layers of the pulmonary arterioles with extension of the muscle layer into the normally non-muscular peripheral arteries has been reported.⁴

The three siblings described presented with cyanosis and respiratory distress soon after birth. Both clinical examination and heart catheterisation showed evidence of pulmonary arterial hypertension with right to left shunting. There was no history of intrauterine exposure to aspirin, indomethacin, or other prostaglandin synthetase inhibitors, nor was there evidence of intrauterine hypoxia, perinatal asphyxia, parenchymal lung disease, myocardial dysfunction, or metabolic abnormalities.

Histological examination of the lung of the three infants showed an appreciable increase in pulmonary arterial smooth muscle and decreased lumen size. The nature and severity of the structural remodelling of the pulmonary arterial bed in these infants suggests that the underlying pathological process was initiated in utero, and that the observed alterations could not have been solely the result of postnatal development. We believe that the structural pulmonary vascular abnormalities described could explain the intractable pulmonary hypertension and the lack of response to medical treatment in the three infants.

None of the clinical conditions commonly associated with persistent pulmonary hypertension of newborn were present in any of the infants and the underlying cause of the development of new muscle

in the walls of the small, normally non-muscular, intra-acinar arteries remains unknown. The parents of these three neonates are first degree cousins and have two other healthy children. This suggests that persistent pulmonary hypertension of newborn due to abnormal muscularisation of the small pulmonary arteries may be a recessively inherited genetic trait.

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Received 26 March 1984

Hyponatraemia in diabetes without ketoacidosis

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SUMMARY At diagnosis six of 18 diabetic children had hyponatraemia with hyperglycaemia but no signs of dehydration or lipaemia. With insulin treatment alone plasma sodium concentrations in two children returned to normal. These children do not require specific treatment to correct the hyponatraemia.

Hyponatraemia is a common finding in both inpatient and outpatient hospital populations.¹ Causes include long term diuretic treatment, renal failure, use of hypotonic intravenous infusion, inappropriate antidiuretic hormone secretion, and

hyperglycaemia.² The latter is a constant feature in the child with newly diagnosed or poorly controlled diabetes. Hyponatraemia may be present when the child is ketoacidotic and severely dehydrated owing to salt and water depletion.³ In the absence of these signs, however, the frequency of hyponatraemia in the diabetic child at diagnosis is unknown.

This study reports a retrospective analysis of the frequency of hyponatraemia in a group of diabetic children at diagnosis, in relation to the presence or absence of ketoacidosis and dehydration.

Patients and methods

The medical records of 18 diabetic children admitted