Chorioamnionitis and serum IgM in Wilson-Mikity syndrome

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SUMMARY A total of 753 infants weighing less than 1800 g at birth were studied prospectively and their serum IgM concentrations measured within 72 hours of age. Placentas from 584 of these infants were examined histologically for chorioamnionitis. The results were correlated with chronic respiratory insufficiency. Altogether 101 infants developed chronic respiratory insufficiency of which 22 had bronchopulmonary dysplasia and 35 Wilson-Mikity syndrome. The remaining 44 infants were classified as 'unexplained chronic lung disease'. Mean serum IgM concentration for Wilson-Mikity syndrome was 1.02 g/l whereas it was 0.14 g/l for bronchopulmonary dysplasia and 0.32 g/l for unexplained chronic lung disease. The incidence of chorioamnionitis was significantly higher in Wilson-Mikity syndrome (30/35) compared with bronchopulmonary dysplasia (4/16) and with infants without chronic respiratory insufficiency (145/490). Wilson-Mikity syndrome was shown to be significantly correlated with the evidences of intrauterine inflammation.

Wilson-Mikity syndrome is a well documented form of chronic respiratory insufficiency of the newborn; the aetiology still remains unsettled. Extensive bacteriological and virological investigations have failed to show a common pathogenic organism.^{1 2} Burnard *et al* considered this syndrome to lie at one end of a spectrum of deranged physiology caused by the mechanical disadvantages in the thorax and airways of immature babies.³

Pathology findings were detailed by Hodgman *et al*.⁴ They performed 10 biopsies and 12 postmortem examinations, and of these 22 cases 12 were studied within 60 days of age. They found areas of hyperinflation and collapse in the first stage, followed by diffuse overinflation during the second stage. Pulmonary fibrosis was found in two cases. No evidence of infection or inflammation was reported.

Our preliminary observations showed that in most infants with Wilson-Mikity syndrome serum IgM measured within 4 days of age was significantly raised.⁵ In the study reported here we investigated the evidence for intrauterine infection preceding Wilson-Mikity syndrome by studying infants with other forms of chronic respiratory insufficiency as controls.

Patients and methods

A prospective study was undertaken of infants admitted to our unit between 1982 and 1986. During this period 1611 infants were admitted of whom 657 infants were ventilated. The overall mortality was 162 (10.1%). There were 181 infants with respiratory distress syndrome of whom 33 (18.2%) infants died.

Altogether 753 infants, who weighed less than 1800 g and who survived for more than six days, were enrolled into the study. We excluded those infants whose neonatal serum samples were not available or who failed follow up to six months. Infants with chronic respiratory difficulty due to upper airway abnormality or poor respiratory drive were also excluded. There were 594 inborn and 159 outborn infants; 370 infants with respiratory distress syndrome or with other respiratory difficulties were ventilated according to the accepted guidelines.⁶ The diagnosis of respiratory distress syndrome was based on clinical signs, chest radiography, and on the assessment of surfactant in gastric or tracheal aspirate using the lecithin:sphingomyelin ratio or microbubble test.⁷ None of the infants with respira-

tory distress syndrome was the subject of artificial surfactant treatment.

Chronic respiratory insufficiency was defined as: prolonged intercostal retractions and a requirement for supplemental oxygen for more than four weeks.⁸ The chest radiographs were interpreted by radiologists without knowledge of the IgM results.

Infants with chronic respiratory insufficiency were subdivided into three groups. The diagnosis of Wilson-Mikity syndrome was made if the infants satisfied the following conditions: absence of respiratory distress syndrome and a chest radiograph showing diffuse, streaky infiltrate with small cystic areas appearing within four weeks.⁴ The criteria for the diagnosis of bronchopulmonary dysplasia was ventilation for respiratory distress syndrome during the early neonatal period and, between 14–35 days of age, a chest radiograph showing at least stage II bronchopulmonary dysplasia.^{9 10} Other infants with chronic respiratory insufficiency for more than four weeks who did not fulfil the criteria for Wilson-Mikity syndrome or bronchopulmonary dysplasia were described as having 'unexplained chronic lung disease'. These babies did not suffer respiratory distress syndrome and did not have radiological changes consistent with Wilson-Mikity syndrome or bronchopulmonary dysplasia.

Cord blood or a blood sample obtained within 72 hours of birth was analysed for serum IgG, IgA, and IgM and measured by radial immunodiffusion (Behring) in duplicate.

The placenta and umbilical cord underwent histological examination: after noting the macroscopic appearance they were fixed in formalin and chorionamnionitis was assessed by polymorphonuclear leucocytic infiltration into the fetal surface of the placenta and graded I, II, or III according to the extent of leucocyte invasion of the chorionic membrane or amniotic membrane respectively.¹¹ The diagnosis of subacute necrotising funisitis was based on the macroscopic and microscopic deposition of necrotic cell debris in the Wharton's jelly around the umbilical vessels. Some samples were calcium positive as shown by the staining of Kossa. The significance of difference in group comparisons was assessed using the χ^2 test with Yates's correction and the Student's *t* test.

Results

Of the 753 infants studied, 101 (13.4%) developed chronic respiratory insufficiency. There were 35 infants with Wilson-Mikity syndrome, 22 with bronchopulmonary dysplasia, and 44 with unexplained

Table 1 Characteristics of infants studied

Group	No of infants (No who died)	Male/Female	Mean (SD) gestation (weeks)	Mean (SD) birth weight (g)	Duration of intermittent positive pressure ventilation		No with respiratory distress syndrome
					No of days	Median (range)	
Wilson-Mikity syndrome	35 (1)	15/20	28.9 (2.3)	1084 (261)	23	5 (0–320)	0
Bronchopulmonary dysplasia	22 (1)	14/8	27.9 (2.6)*	937 (315)*	22	13 (3–74)	22
Unexplained chronic lung disease	44 (3)	29/15	27.4 (2.6)	917 (280)	37	29 (0–90)	0
Others†	652 (18)	291/361	31.2 (2.9)	1336 (300)	288	3 (0–100)	109

**p*<0.01.

†Infants weighing <1800 g, who survived for more than six days, and who did not have chronic respiratory insufficiency.

Table 2 Serum IgM, IgG, and IgA concentrations within 72 hours of age (g/l)

Group	IgM*		IgG		IgA	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Wilson-Mikity syndrome	1.02–(1.04)	0.06–3.77	5.80–(2.00)	2.72–11.52	0.05 (0.09)	0–0.44
Bronchopulmonary dysplasia	0.14–(0.08)	0.05–0.31	5.52–(2.06)	2.41–9.63	0.02 (0.05)	0–0.23
Unexplained chronic lung disease	0.32–(0.42)	0.05–1.79	4.83–(1.84)	1.72–8.80	0.03 (0.08)	0–0.39
Others*	0.21–(0.35)	0.02–3.46	7.16–(2.73)	1.80–19.14	0.01 (0.05)	0–0.47

*Wilson-Mikity syndrome compared with bronchopulmonary dysplasia, unexplained chronic lung disease, and others: *p*<0.001.

†Infants weighing <1800 g, who survived for more than six days, and who did not have chronic respiratory insufficiency.

Table 3 Association between chorioamnionitis, subacute necrotising funisitis, and chronic lung disease

Group	Absent	Chorioamnionitis			Subacute necrotising funisitis	
		I	II	III	Absent	Present
Wilson-Mikity syndrome	5	0	6	24*	18	17†
Bronchopulmonary dysplasia	12	2	2	0	16	0
Unexplained chronic lung disease	10	4	7	22	42	1
Others‡	345	32	54	59	477	13

Values indicate number of cases. The sample number available for analysis was 584 among 753 infants studied.
 *Wilson-Mikity syndrome compared with bronchopulmonary dysplasia and Wilson-Mikity syndrome compared with others: $p<0.001$.
 †Wilson-Mikity syndrome compared with other group: $p<0.001$. ‡Infants weighing <1800 g, who survived for more than six days, and who did not have chronic respiratory insufficiency.

chronic lung disease. Their characteristics are shown in table 1, together with infants without chronic respiratory insufficiency. Infants with unexplained chronic lung disease were more preterm and of lower birth weight compared with infants with Wilson-Mikity syndrome.

The mean serum IgM concentration within 72 hours of age was significantly higher in the group with Wilson-Mikity syndrome compared with the other individual groups ($p<0.001$) (table 2). No differences were found in serum IgG or in IgA between each group or in IgM between the groups without Wilson-Mikity syndrome.

The placenta and cord were available for analysis in 584 (78%) infants. They were examined for inflammatory changes. The group with Wilson-Mikity syndrome had a significantly higher incidence of chorioamnionitis than the group with bronchopulmonary dysplasia or those without chronic respiratory insufficiency ($p<0.001$) (table 3).

Subacute necrotising funisitis has been shown to correlate with intrauterine infection and with chorioamnionitis.¹² In the subjects studied the incidence of subacute necrotising funisitis was significantly higher in the group with Wilson-Mikity syndrome ($p<0.001$) (table 3).

Discussion

We believe this is the first study of the association between immunoglobulin concentrations, placental pathology, and chronic respiratory insufficiency.

Serum IgM has been shown to be within a limited range both for term and preterm neonates.¹³ Its increase indicates intrauterine infection. In established intrauterine infection such as cytomegalovirus and rubella there is a rise of total serum IgM and specific IgM concentrations.

The association of chorioamnionitis and subacute necrotising funisitis with intrauterine infection has

been well established, and is presumably due to ascending infection.¹⁴ The increased incidence of chorioamnionitis and subacute necrotising funisitis in infants with Wilson-Mikity syndrome is further evidence of intrauterine infection.

Chorioamnionitis is common in preterm births but a high serum IgM does not always accompany chorioamnionitis. The incidence of chorioamnionitis correlates inversely with gestational age of birth, but IgM correlates neither with gestational age nor with chorioamnionitis.¹⁵ The association between total IgM and chorioamnionitis is therefore not fully explained. The event which initiated the pathology in the fetus and the placenta for Wilson-Mikity syndrome might be a different one from that which causes the chorioamnionitis seen in unexplained chronic lung disease or in general preterm births.

The second point to be raised in this study is the difference in the incidence of chorioamnionitis between bronchopulmonary dysplasia and unexplained chronic lung disease. The original concept of bronchopulmonary dysplasia reported by Northway *et al* in 1967 was association with respiratory distress syndrome during the early neonatal period.⁹ After the recognition of a group of infants who show similar chronic lung disease without respiratory distress syndrome the concept was expanded.¹⁶ It is not known if there were any differences in the aetiology between those infants with and without respiratory distress syndrome. It is made clear in the present study that there is an important group of babies with chronic respiratory insufficiency who do not have typical radiological changes of Wilson-Mikity syndrome or bronchopulmonary dysplasia. Combined with the high incidence of chorioamnionitis in these infants, we speculate that the chorioamnionitis may be the predisposing factor in the aetiology of unexplained chronic lung disease. The possible mechanism of chorioamnionitis relating to chronic lung insufficiency is discussed below.

The incidence of Wilson-Mikity syndrome in

western countries has been reported to be much less in recent years. This is not the case in Japan, and 4.8%–8.7% of infants born weighing less than 1500 g have been reported to have Wilson-Mikity syndrome.^{17, 18} There are two possible explanations for this: the first is that the real incidence has become low in western societies, and the second could be that some cases of existing Wilson-Mikity syndrome are misdiagnosed and confused with other groups of chronic lung disease, particularly with bronchopulmonary dysplasia. It is not surprising that a disease of an ill defined nature like Wilson-Mikity syndrome can still go unrecognised.

Infants with Wilson-Mikity syndrome show an uneven distribution of air spaces throughout their lungs and establish typical emphysema in the first several weeks of life. The pathophysiological lesion of the syndrome lies in the terminal airways, as shown by several lung function studies.^{19–21} Then what is the relevance of the high incidence of chorioamnionitis and increased serum IgM in these infants? In this context recent findings on neutrophil elastase in pulmonary emphysema may be important.^{22, 23} As destruction of elastin and the concomitant loss of elastic recoil in the emphysematous lung have been well established, attention has been focused on elastase as the primary destructive agent in the pathogenesis of emphysema. We have shown that the fetus who later developed Wilson-Mikity syndrome was subjected to chorioamnionitis. It is reasonable to expect that in response to chorioamnionitis the neutrophils migrate into the airway down to the developing alveoli. The rise in serum IgM concentration may be the immunological response of the fetus to infection. In our preliminary observations we found an increase in the number of neutrophils in the tracheal aspirate of the newborns who later developed Wilson-Mikity syndrome.²⁴ The numbers of neutrophils in the amniotic fluid were also high. In the same infants high neutrophil elastase was found in the tracheal aspirate obtained in the first 12 hours of birth. The difference was significant compared with those of preterm infants without respiratory illness and with respiratory distress syndrome. We therefore speculate that, whatever the triggering factor may be, invasion of neutrophils is involved. The increased elastase overwhelms the fetal antiproteinase activity, then hydrolyses the elastin that maintains the patency of terminal airways. After the postnatal adaptation for extrauterine life, these infants then develop pulmonary emphysema a few days and weeks after birth.

It seems that chorioamnionitis alone is not enough to cause Wilson-Mikity syndrome. The raised serum IgM suggests that the fetus has made an immuno-

logical response. Infants with unexplained chronic lung disease showed little increase in serum IgM. It is therefore a possibility that this difference in IgM between Wilson-Mikity syndrome and unexplained chronic lung disease correlates with a variety of clinical pictures. It also remains to be clarified if the aetiology of chorioamnionitis is the same in Wilson-Mikity syndrome and unexplained chronic lung disease.

In conclusion, we have shown that Wilson-Mikity syndrome can be defined as a form of chronic respiratory insufficiency characterised by a raised neonatal serum IgM concentration and associated with chorioamnionitis. Wilson-Mikity syndrome should be clearly differentiated from bronchopulmonary dysplasia so as to contribute to the further understanding of chronic respiratory insufficiency of newborn infants.

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Accepted 15 May 1989