Wilson-Mikity Respiratory Distress Syndrome

C. H. SINNETTE, A. M. BRADLEY-MOORE, W. P. COCKSHOTT,
and G. M. EDINGTON

From the Departments of Paediatrics, Radiology and Pathology, University College Hospital, Ibadan, Nigeria

In 1960 Wilson and Mikity described a new form of respiratory disease in seven premature infants. In these infants the disease developed insidiously a few days or a few weeks after birth and was characterized by marked cyanosis, tachypnoea, exertional dyspnoea, wheezing, and coughing. All patients showed distinctive radiological changes. Clinical recovery always preceded resolution of the radiological changes, sometimes by several months.

Since the original report from the United States of America, additional cases have been reported from Europe and other parts of the North American Continent, and a total of 32 cases has been reported to date.

This report describes two premature infants born at the University College Hospital, Ibadan, who showed findings typical of the syndrome described by Wilson and Mikity. The second case showed features that hitherto have not been recorded.

Case Reports

Case 1. This baby boy was delivered spontaneously as a vertex presentation at 31 weeks' gestation to a 34-year-old Nigerian multigravida. During this pregnancy the mother had recurrent episodes of painless vaginal bleeding from the eighth week onwards despite bed-rest and sedation.

The infant weighed 1251 g. at birth and appeared in good general condition except for considerable moulding of the skull bones and a high-pitched cry which disappeared after several hours. A loud pansystolic murmur was heard over the praecordium and radiated to the back. The other systems were normal. He was given a five-day course of penicillin and streptomycin, as there was a possibility that the membranes had ruptured three weeks before delivery.

His condition remained satisfactory apart from mild jaundice which was noted on the 3rd day and which had completely disappeared by the 7th day. The cardiac murmur was gone by the 20th day and the infant was gaining weight.

On the 24th day he became irritable and dyspnoeic. Scattered crepitations were heard at the base of the left

lung. A chest x-ray film taken at this time showed generalized fine mottling which was thought to be a bilateral bronchopneumonia. A lumbar puncture showed normal CSF. Penicillin and streptomycin were started again and oxygen was administered in an incubator. Throughout the day the dyspnoea persisted and he had several cyanotic attacks.

The following day he showed further evidence of respiratory distress, with marked sternal and costal recession. Apnoeic episodes occurred frequently and he became intensely cyanosed during these episodes. The breath sounds were vesicular with scattered crepitations heard bilaterally. At this time tetracycline was added.

A blood culture taken on the 24th day was later reported as showing a growth of coagulase-positive staphylococci. At this time erythromycin was started and the other antibiotics were discontinued. There was no improvement with erythromycin. Antituberculous treatment was started when it was suspected that the mother had pulmonary tuberculosis. After 17 days the antituberculous drugs were discontinued without any change in the patient's condition.

Repeat x-ray films on the 45th day showed a diffuse, ill-defined lace-like pattern throughout the lung fields, which suggested the possibility of the Wilson-Mikity syndrome. The dyspnoea and apnoeic attacks persisted despite constant nursing in oxygen. Framycetin and steroids failed to alter the progressively downhill course and the patient died on the 59th day.

Necropsy. A well-pigmented, small baby weighing 2050 g. There was moderate lanugo and there were depigmented patches over the groins. There were no superficial petechiae, no jaundice, and no anaemia. The umbilical cord was detached and the stump was dry. Both testes were descended.

The gastro-intestinal tract, the reticuloendothelial system, the genito-urinary system, and the central nervous system were normal.

The heart weighed 22 g. There was no pericardial effusion and the ductus was closed. There were a few petechiae over the anterior surface of the heart and the right atrium was distended with blood. The right ventricular wall measured 4 mm. in thickness and the left measured 5 mm. The valves were normal as were the great vessels. The foramen ovale was widely patent.

There was no debris in the trachea. Both pleural cavities were free of fluid and the fissures of both lungs

FIG. 1.—Case 1. Lungs, showing the uneven expansion of the tissues with post-mortem inflation.

were complete. The surface of the lungs was mottled with dark red and pale red areas. Fine petechiae studded the lung surface. Raised areas of white emphysematous lung tissue several millimetres in diameter were found throughout both lungs but mainly in the lower lobes. The left lower lobe felt firmer than the other lobes. The lungs were inflated gently and it was noted that the resulting expansion was not uniform. Some segments of the lung expanded and became raised nodules while other segments remained unexpanded (Fig. 1). The over-all appearance was like a cirrhotic liver. On section there was little congestion. There were expanded aerated areas interposed by dull red solid areas of lung tissue. No evidence of recent abscess formation was noted.

Histology. The heart was not remarkable. There was mild fatty infiltration of the liver with scanty foci of extramedullary erythropoiesis. No chronic venous congestion was seen.

The histological appearances of the lungs were varied (Fig. 2). In some areas there was conspicuous thickening of the alveoli, occasionally with a concomitant extravasation of red blood cells. Cystic emphysematous areas were present at the periphery of the abnormal alveoli. In other areas collapse had occurred. The larger vessels and bronchi appeared normal. There was no evidence of gross infection and inclusions were not seen.

Post-mortem comment. The macroscopic and microscopic appearances of the lungs and their response to inflation were compatible with a diagnosis of the Wilson-Mikity syndrome (Fig. 1 and 2).

Case 2. This baby girl was delivered spontaneously as a vertex presentation at 28 weeks' gestation to an 18-year-old Nigerian primigravida. Delivery was precipitate and occurred in the Casualty Department of

University College Hospital, Ibadan. During the pregnancy the mother was well apart from a mild unspecified fever and rash which occurred during the first trimester. There was no history of vaginal bleeding during the pregnancy though on admission to the lying-in ward the mother was found to be anaemic (PCV 27%).

The infant weighed 948 g. at birth. She cried lustily and was lively. Colour was good and no abnormal physical findings were detected. She was nursed in an incubator and oxygen was discontinued after a few hours. Feeds given by indwelling catheter were retained without difficulty and her condition remained satisfactory.

On the 4th day, the infant became slightly cyanosed and developed some sternal recession. Her weight at this time was 778 g. She was nursed in oxygen and a course of penicillin and streptomycin was started.

Over the next two days dyspnoea became more marked. There was severe distress on exertion, with gross recession of the sternum, ribs, and suprasternal tissues. On the 6th day, she had several apnoeic attacks. No adventitious sounds were heard and there was no evidence of heart failure. On the 7th day steroids were started. A chest x-ray film taken on the 8th day showed generalized hyperaeration and a bilateral diffuse infiltration of a coarse reticular pattern. This appearance was compatible with the Wilson-Mikity syndrome.

On the 11th day the patient began to improve and, though marked recession was still present, she required less oxygen to maintain a good colour. Her weight had fallen to 736 g. by this time.

Chest x-ray films, repeated on the 14th day, showed marked changes in the lungs with the typical streaky pattern radiating from the hilar regions and most pronounced in the upper lobes (Fig. 3). A haemogram on the 15th day showed a leucocytosis (39,000/c.mm.) with 63% neutrophils and 21% lymphocytes. One week later the leucocytosis was less marked (16,000/c.mm.). Electrocardiograms taken on the 16th and 37th days showed slight right ventricular preponderance. Numerous urinalyses did

FIG. 2.—Case 1. Histological appearance of lung tissue showing areas of normal alveoli, cystic emphysematous areas with thickened alveolar walls, and extravasation of red blood corpuscles and histiocytes. ($\times 96$.)

not reveal the presence of inclusion bodies. Repeated determinations of the serum electrolytes were normal (the blood pH was not measured).

The infant continued to maintain satisfactory progress. By the 26th day steroids were discontinued and by the

27th day oxygen was no longer necessary. The lungs were clinically clear and the recession had disappeared. Breast-feedings were started at the age of 4 weeks.

A type 7 ECHO virus was isolated from a throat swab taken on the 46th day. A repeat chest x-ray film taken on the 53rd day showed considerable improvement (Fig. 4). Tomograms taken at this time were normal.

FIG. 3.—Case 2. Radiograph showing the development of coarse streaking in the lung fields most marked in the upper lobes.

FIG. 4.—Case 2. Radiograph showing clearing of the lung fields.

The infant was discharged on the 73rd day weighing 2500 g. There were no abnormal physical signs and she appeared to have made a complete clinical recovery. Chest x-ray films taken on the day of discharge showed further resolution of the radiological changes.

The infant continued to do well, but 13 days after discharge she was brought back to the hospital moribund and died shortly after admission. The only history that was obtained was that the infant had stopped sucking 48 hours earlier.

Necropsy. An anaemic Nigerian female weighing 2390 g. and measuring 45 cm. in length.

Macroscopically the brain appeared normal. The larynx and trachea were pale. The pleural cavities were normal. The pleural surfaces of both lungs were smooth and glistening with a number of subpleural haemorrhages. There were numerous depressed red areas in all lobes which on section extended into the lung parenchyma. The bronchi and pulmonary vessels were unremarkable. There was mild hypertrophy of the right ventricle. No abnormality was noted in the abdominal organs apart from dilatation of the middle third of the left ureter for which no anatomical cause could be found.

Histology. The main findings were confined to the brain and lungs. In the brain there was widespread lymphocytic infiltration of the meninges without extension to the parenchyma.

There were patchy areas throughout all lobes of the lungs, showing thickening of the alveolar septa with numerous areas of collapse and 'compensating' emphysema. The areas of collapse appeared to follow the line of the larger blood vessels. Histiocytes were present in the alveoli with the thickened walls, but were absent in the expanded and emphysematous areas. No giant cells or inclusion bodies were noted. A patchy epithelial lining could be discerned in a number of the thickened alveolar walls. Blood vessels were numerous. No increase of reticulin or elastica was noted with appropriate staining methods.

Post-mortem comment. The causes of death were lymphocytic meningitis and the Wilson-Mikity syndrome. Post-mortem specimens of blood, trachea, heart, lung, and liver were taken for virological investigation. No virus was isolated from these specimens. Brain tissues unfortunately was not included in the virological investigations.

Discussion

The report of Wilson and Mikity (1960) described a new abnormality of the newborn, in which respiratory distress and cyanosis were the principal presenting symptoms and in which there was a characteristic radiological appearance. The eponymous term of Wilson-Mikity is used in this report, since there is no general agreement on the histological terminology.

In the original report, 7 cases were described and

in all of them the mothers had a history of vaginal bleeding during pregnancy. However, in the later reports, maternal vaginal bleeding was not a common feature. Of the cases reported to date, only one infant was born at full term. All the others were born prematurely. As noted in hyaline membrane disease, it appears that the Wilson-Mikity respiratory distress syndrome has a distinct predilection for infants of low birthweight and low gestational age.

The aetiology of this disease remains obscure. Bacteriological examinations in the reported cases have failed to demonstrate a common organism which could be consistently recovered from nasopharyngeal or blood cultures. A coagulase-positive staphylococcus was grown on one blood culture in Case 1 but was not recovered on subsequent cultures. While antibiotic treatment may have prevented recovery of the organism on subsequent cultures, the clinical course, the radiological appearance, and the post-mortem findings were not compatible with a staphylococcal pulmonary infection. The short-lived leucocytosis in Case 2 may have been due to a transitory infection which more than likely was unrelated to the pulmonary pathology. A type 7 ECHO virus was isolated from the nasopharynx in Case 2. This is the second reported instance in which an enterovirus has been isolated in a patient with this syndrome. Butterfield, Muscovici, Berry, and Kempe (1963) reported an outbreak of respiratory illness among 8 premature infants, 4 of whom showed radiological evidence of the Wilson-Mikity syndrome. In one of the 4 infants so affected, a type 19 ECHO virus was isolated from a post-mortem specimen. The recovery of an enterovirus during the course of the illness in Case 2 and the subsequent development of a lymphocytic meningitis may or may not have been coincidental.

The course of the disease is variable (Fig. 5 and 6). The onset of symptoms may be noted at birth but may not appear until as late as 5-6 weeks of age. Signs of respiratory obstruction are usually pronounced. Cyanosis appears to be a fairly constant feature and may be very marked. Congestive cardiac failure has been reported and is associated with right heart overload. Respiratory acidosis has been observed and in the series described by Swyer, Delivoria-Papadopoulos, Levison, Reilly, and Balis (1965), the decreased arterial oxygen saturation suggested the possibility of an intrapulmonary shunt. Clinical recovery in the survivors precedes resolution of the radiological appearances which in some cases persist for many months. Of the 32 cases thus far described, 12 patients have died.

In both patients reported in this paper, the radiological appearances were diagnostic, conform-

FIG. 5.—Case 1. Hospital course showing the late onset and long duration of the illness. Note the persistent dependence on oxygen throughout the disease and the poor response to antibiotics.

ing to the patterns reported by Wilson and Mikity (1960), Baghdassarian, Avery, and Neuhauser (1963), and Grossman, Berdon, Mizrahi, and Baker (1965). In Case 1 a diffuse change was shown in the x-ray film

of the right lung. Later multiple small round focal areas of hyperaeration were present, particularly at the bases. This finding was combined with coarse streaking of the lung parenchyma, which was most

FIG. 6.—Case 2. Hospital course showing the early onset of the illness, the brief duration of symptoms and signs, and the apparently complete clinical recovery.

evident in the upper lung fields. A fortnight later, the parenchymal streaking was much more obvious and the focal cystic areas had disappeared. The heart was not enlarged and the pulmonary vascularity was within the limits of normality.

The second patient showed a similar sequence of changes, starting with focal areas of hyperaeration most marked at the bases. As these areas slowly resolved, coarse streaking developed (Fig. 3), finally leading to clearing of the lung fields (Fig. 4). The focal cystic areas coexisted with the coarse diffuse reticular infiltrates for a period, and there was generalized hyperaeration.

This pattern of evolution has been noted by previous workers. Grossman *et al.* (1965) have suggested that these radiographic phases can be separated into an acute period with lucent foci associated with a reticular pattern; an intermediate stage during which the coarse streaks are the dominant feature; and a final stage in which the lung fields revert to a normal appearance. In our cases the radiographic changes followed this pattern but only the second patient attained the final stage.

The pathological findings are equally striking and correlate closely with the radiological appearance. The lungs are often larger than expected and show areas of hyperaeration. On inflation the hyperaeration is more pronounced and produces an uneven distribution over the lung surface, resembling the 'hobnail' appearance of the cirrhotic liver.

On microscopic examination, there is marked thickening of the alveolar septa and cystic emphysematous changes. Histiocytes and mononuclear cells are often found in the alveolar spaces. Recent electron microscopy findings suggest that the capillary network is incompletely developed (Swyer *et al.*, 1965). These findings tend to support the contention of those who believe that the lesion is primarily one of dysmaturity rather than emphysema.

The differential diagnosis of respiratory distress in the newborn must, of necessity, include hyaline membrane disease. It is extremely difficult at the onset to differentiate between hyaline membrane disease and the Wilson-Mikity syndrome. The clinical course and radiological changes will assist in clarifying the diagnosis. In retrospect, many of the earlier radiological descriptions of patients with hyaline membrane might well fit into the radiological classification of the Wilson-Mikity syndrome, and the disease may be more common than present reports indicate.

Systemic diseases, such as tuberculosis, mucoviscidosis, cytomegalic inclusion body disease, protozoan and fungal diseases have been systematically

excluded in the published cases. Other types of pulmonary infiltration, such as diffuse interstitial fibrosis (Hamman-Rich syndrome), familial fibrocystic lung disease, and reticuloses may show a somewhat similar x-ray appearance, but the associated features and different clinical course will assist in making the diagnosis.

Treatment is symptomatic. Nursing in oxygen is necessary to relieve the hypoxia. Digitalization is indicated in cases of congestive cardiac failure. Antibiotics do not appear to affect the course of the disease, and their use is only warranted for intercurrent infection. Likewise, steroids have not been shown to be of value and their role in preventing subsequent fibrosis is doubtful.

Summary

Two premature infants with the Wilson-Mikity respiratory distress syndrome are presented. Both showed features typical of this syndrome including prematurity, variable onset of symptoms, cyanosis, rib recession, and dyspnoea.

The x-ray films revealed characteristic changes of an acute stage with lucent areas associated with a reticular pattern, an intermediate stage during which coarse streaks appeared, and a final stage in which the lung fields returned to normal.

A type 7 ECHO virus was isolated from a nasopharyngeal swab taken from the second patient.

One infant died during the acute stage of the illness but the other infant recovered clinically and radiologically, only to die unexpectedly two weeks after discharge from hospital. In both cases, necropsy confirmed the diagnosis.

The aetiology of the disease is obscure and treatment is symptomatic.

The authors wish to thank Professor R. G. Hendrickse for his kind permission to publish Case 1 from his Unit; Professor D. Montefiore for his assistance in the virological investigations; and the Medical Illustration Unit, University College Hospital, Ibadan, for their invaluable assistance in the preparation of the diagrams and photographs.

REFERENCES

- Baghdassarian, O. M., Avery, M. E., and Neuhauser, E. B. D. (1963). A form of pulmonary insufficiency in premature infants. Pulmonary dysmaturity? *Amer. J. Roentgenol.*, **89**, 1020.
- Butterfield, J., Muscovici, C., Berry, C., and Kempe, C. H. (1963). Cystic emphysema in premature infants. A report of an outbreak with the isolation of type 19 ECHO virus in one case. *New Engl. J. Med.*, **268**, 18.
- Grossman, H., Berdon, W. E., Mizrahi, A., and Baker, D. H. (1965). Neonatal focal hyperaeration of the lungs (Wilson-Mikity syndrome). *Radiology*, **85**, 409.
- Swyer, P. R., Delivoria-Papadopoulos, M., Levison, H., Reilly, B. J., and Balis, J. U. (1965). The pulmonary syndrome of Wilson and Mikity. *Pediatrics*, **36**, 374.
- Wilson, M. G., and Mikity, V. G. (1960). A new form of respiratory disease in premature infants. *Amer. J. Dis. Child.*, **99**, 489.