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Usefulness of the Acute Phase Reactants (APR) score (Part 2): Characteristics of the APR-Score in Wilson-Mikity Syndrome

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ABSTRACT

Background: The etiology of Wilson-Mikity syndrome (WMS) remains uncertain. Inflammation of the fetal lung caused by intrauterine infection spilling over into the lungs results in lung tissue collapse and birth before complete repair is achieved. Continued spontaneous breathing exacerbates lung damage that results in the development of chronic lung disease.

Objective: To investigate whether the acute phase reactants score (APR-Sc) can help in the early postnatal diagnosis of WMS.

Subjects and Methods: Twenty-two patients with WMS had their APR-Sc measured in cord blood or in infant blood within 1 hour after birth, and we examined the breakdown of the APR-Sc and its relationship to placental pathology and IgM levels.

Results: Of the 22 WMS cases, 18 (82%) had an APR-Sc of 0, and none had an APR-Sc of 3 or 2 (CRP and AGP both positive) in the acute phase of infection. All had chorioamnionitis, 17 (77%) had funisitis, and only 8 (40%) were positive for IgM.

Conclusions: Our results suggest that preterm infants with WMS have already passed the acute stage of inflammation in utero. The APR-Sc should be measured in cord blood or early postnatal blood of preterm infants requiring ventilatory management, and if the APR-Sc is 0 to 1, spontaneous respiration in high frequency oscillation mode should be temporarily discontinued to promptly heal fetal lung injury in consideration of WMS complications. Thus, the APR-Sc can help in the management of WMS.

Keywords: APR Score; Chronic Lung Disease; Fetal Inflammatory Response Syndrome; Funisitis; Wilson-Mikity Syndrome

Introduction

Wilson-Mikity syndrome (WMS), first described in 1960 [1], predates 1967, when the concept of chronic lung disease (CLD) was first described by Northway et al. under the name bronchopulmonary dysplasia [2]. Subsequently, WMS became one of the important diseases belonging to CLD. As a result of remarkable developments in neonatal medicine, such as that of artificial lung surfactants and the improvement of artificial mechanical ventilators dedicated to premature newborns, the survival rate of pathological newborns has improved significantly. As a result, there have been some reports of changes in the clinical picture of WMS. In Japan, the definition and classification of CLD was established in 1989 by the "Chronic Lung Disease Research Group" as a part of the Ministry of Health and Welfare's research on mental and physical disorders [3]. This classification system divides CLD into seven types ranging from type I to VI that are characterized by the presence or absence of a bubbling/

cystic appearance on chest X-ray as an indicator of the severity of respiratory distress, the presence or absence of intrauterine infection (inflammation), and respiratory distress syndrome (RDS). A confirmed diagnosis of WMS is classified as type III CLD, and a suspected diagnosis is classified as type IV CLD (Table 1). In clinical practice, there is a demand to know how early the onset of CLD can be predicted and how to prevent its onset. Therefore, the classification of CLD established in Japan is not only necessary for diagnosis but is also useful for determining the type of progression and initiating preventive methods.

Table 1: Classification of neonatal CLD in Japan.

Type	RDS	Intruterine infection/inflammation	Bubbly/cystic appearance
I	+	-	+
II	+	-	-
III	-	+	+
III′	-	+	-
IV	-	ND	+
V	-	-	-
VI	ND	ND	ND

Note: CLD: Chronic Lung Disease; ND: No Data; RDS: Respiratory Distress Syndrome

Currently, the pathogenesis of WMS is infection of lung tissue by certain pathogens in the uterus or an inflammatory response of the lungs during intrauterine infection, and histopathological studies have reported that the acute phase of inflammation may have already passed by the time of birth [4]. In principle, histopathological diagnosis requires a series of processes in which a specimen is first formalin-fixed and embedded in paraffin, then slide specimens are prepared, and the results of the microscopic examination are awaited. If early postnatal differentiation at the bedside is possible, it may have the benefit of increasing eligibility of the infant to be treated by various methods, especially respiratory management. Forty years ago, we developed the acute phase reactants score (APR-Sc), which simultaneously measures three of the APRs, C-reactive protein (CRP), α1-acid glycoprotein (AGP), and haptoglobin (Hp), and scores them according to the presence of elevations in each [5]. We now have a dedicated instrument that can measure each substance in a 10-μL serum sample for each APR and complete the measurement in about 3 minutes. The lungs at birth in infants with WMS present immature lung tissue destroyed by inflammation, which is clearly different from the process of progression of immature lungs in the RDS classification of CLD. Therefore, it is not surprising that treatment strategies are different in postnatal respiratory management, and it is valuable to determine immediately after birth whether a premature infant who does not develop RDS will subsequently develop WMS. We hypothesized that the characteristics of the APR-Sc may help in the diagnosis of the onset of WMS.

Patients and Methods

Preterm infants admitted to the Japanese Red Cross Musashino Hospital and Nagoya City University Nagoya West Medical Center NICU with a diagnosis of WMS during the 11 years and 6 months from January 2011 to June 2022, and whose APR-Sc could be calculated by measuring APRs in cord blood or blood drawn from each infant within 1 hour after birth were included in the study. The clinical diagnostic criteria for WMS were as follows [6].

1. Preterm infants with non-RDS,
2. Intercostal retraction or tachypnea lasting more than 4 weeks,
3. Appearance of diffuse small round areas of emphysema (so-called bubbling) on their chest X-ray at least twice within 8 weeks of birth,
4. High IgM levels of 30 mg/dL or more in cord blood or early postnatal blood, or
5. Findings of chorioamnionitis (CAM) or umbilical cord inflammation (funisitis) are observed in the placental pathology. Currently in Japan, a definitive diagnosis of WMS corresponds to CLD type III, and a suspected diagnosis corresponds to CLD type IV in terms of CLD extending beyond 28 days of age (CLD28) [7].

The pathological diagnosis was made by a pathologist who was blinded to all information about the child except for gestational age, birth weight, and the obstetrician's request for the specimen. The histological description of CAM was based on the Blanc classification [8], whereas that of funisitis was classified as Stage I if infiltrating leukocytes were confined to the vascular endothelium, Stage II if they extended to the vascular muscularis, and Stage III if they infiltrated Wharton's collagen [9]. For calculation of the APR-Sc, a machine dedicated to this purpose, the Latessier TM (SHINOTEST, Sagamihara, Japan), was used, in which 10 μL of serum was sufficient to measure

each of the three APRs (CRP, AGP, and Hp). In our experience, 80 μL of whole blood centrifuged from a single capillary used to measure jaundice is sufficient for the measurement of preterm infants with hematocrit values ≤ 60%, unless the subject is very polycythemic. When the birth weight of the infant and the age on the day of measurement are first entered, the device recognizes the three APR reference values at that time, calculates one point if the upper limit of the reference value is exceeded, zero if not, and finally gives the result as a total score for the three APRs of 0 to 3 points. A sensor-equipped micropipette fitted with a special tip that allows direct aspiration of serum from centrifuged capillaries is included; CRP is automatically measured using the latex immunoturbidimetric method, and AGP and Hp are measured using the immunoturbidimetric method. Calculation time for the three APRs is as short as 30 seconds, 60 seconds, and 60 seconds, respectively, and if the test tubes containing reagents for instillation are incubated in advance, results can be obtained in about 3 minutes from input to calculation of results. The compact measuring device can be used to measure APRs in infants in real time at the bedside, and the measurement ranges for CRP, AGP, and Hp in the APR-Sc calculation mode are 0.25~15.0 mg/dL, 20~300 mg/dL, and 20~300 mg/dL, respectively. In addition, scoring for the subjects of this study, preterm low birth weight infants of day 0, was as follows: CRP of ≥ 0.3 mg/dL: 1 point; AGP of 20 mg/dL or higher if birth weight is <1000 g and 30 mg/dL or higher if birth weight is ≥1000 g: 1 point, and Hp up to 13 mg at birth or 13 mg/dL or higher up to 72 hours after birth: 1 point. Bacterial infection is diagnosed when the APR score is 3 points or each of CRP and AGP is 1 point. Figure 1 shows the temporal trend of the APR-Sc when a patient develops a bacterial infection. The course of a series of bacterial infections is classified into three phases. The combination of which of the three APRs is positive can be used to determine which stage of the infection the infant is currently in.

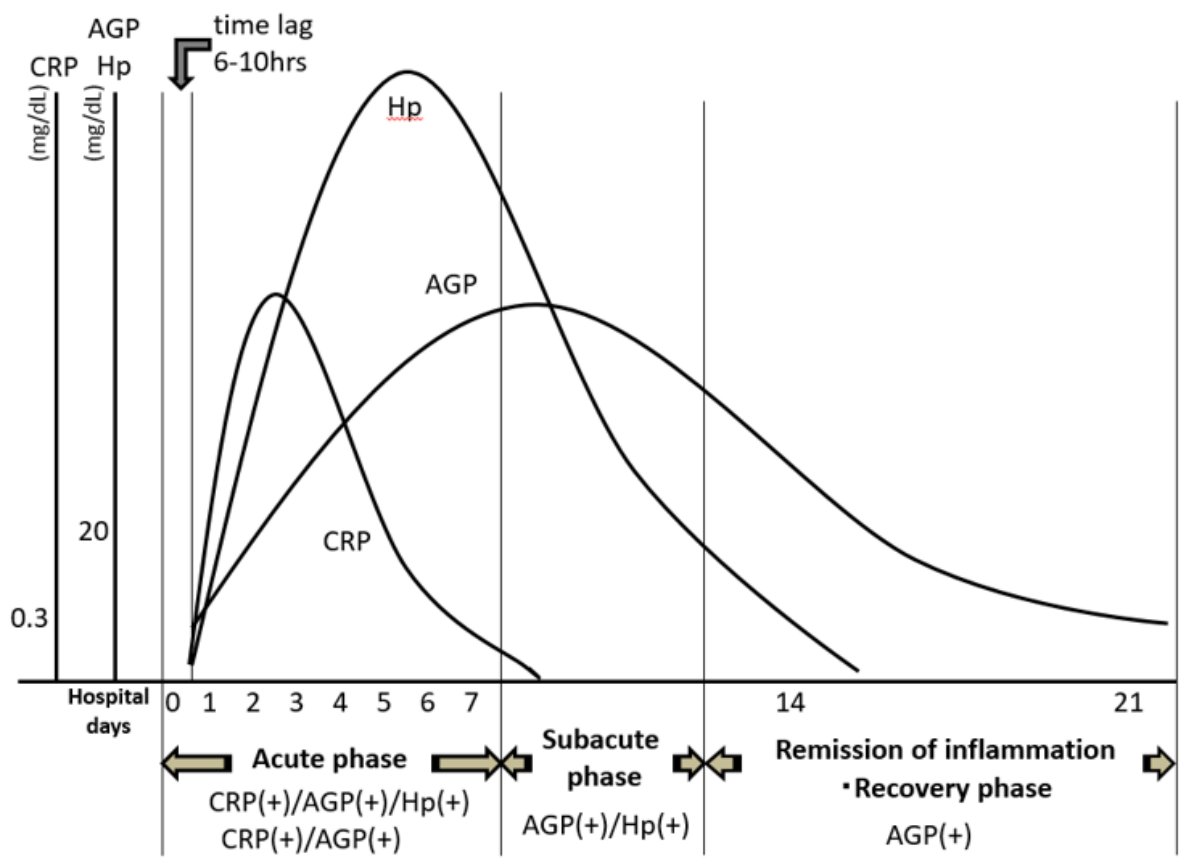

Figure 1: Schematic diagram of time course of acute phase reactant proteins in early neonatal periods with either intrauterine infection or fetal inflammatory response syndrome. It can be seen that infant with WMS correspond to the subacute phase or recovery phase at birth.

Table 2: Patients' profiles.

Case	GA (weeks)	BW (gr)	Amniotic turbidity	PROM>18hr	CAM	FN	APR CRP (mg/dL)	AGP (mg/dL)	Hp(mg/dL)	IgM(mg/dL)
1	28	1130	+	-	III	3	<0.3	<20	<13	135
2	25.29	650	+	6days	III	3	<0.3	26	31	ND
3	27.86	765	+	-	III	3	0.3	33	<13	<30
4	27.14	907	+	-	III	3	<0.3	<20	<13	<30
5	25.29	720	-	-	III	3	<0.3	<20	<13	<30
6	25.71	679	-	4days	III	3	<0.3	<20	45	<30
7	25.86	812	+	-	III	3	<0.3	<20	<13	<30
8	26.86	888	-	20hr	III	3	<0.3	<20	<13	42.4
9	24.71	627	+	-	III	1	<0.3	<20	<13	54.5
10	28.14	896	+	-	III	1	<0.3	<20	<13	198.7
11	26.71	849	+	-	III	-	<0.3	<20	<13	<30
12	29.57	1360	-	-	II	3	<0.3	<20	<13	39
13	24.42	710	-	2days	II	3	<0.3	<20	<13	ND
14	27	1220	+	-	II	3	<0.3	<20	<13	52
15	27	872	-	-	II	3	<0.3	<20	<13	49
16	25.57	986	+	-	II	2	<0.3	<20	<13	104
17	24.86	684	-	-	II	2	<0.3	<20	<13	<30
18	26	946	+	-	II	-	<0.3	<20	<13	<30
19	28.29	1320	-	-	I	1	0.3	32	<13	93
20	25.29	842	+	-	I	-	0.54	<20	<13	<30
21	26	748	-	-	I	-	<0.3	<20	<13	<30
22	36.14	2654	-	-	I	-	<0.3	57	115	49.6

Note: GA: Gestation Age; BW: Birth Weight; PROM: Premature Rupture of Membrane; CAM: Chorioamnionitis; FN: Funisitis; APR: Acute Phase Reactants; CRP: C-Reactive Protein; AGP: α1-Acid Glycoprotein, Hp: Haptoglobin.

Results

Twenty-two preterm infants diagnosed as having clinical WMS at the two centers were included. Gestational age ranged from 24 weeks 3 days to 36 weeks 6 days (median 26 weeks 0 days). Birth weights ranged from 627 g to 2654 g (median 849 g). Amniotic fluid turbidity was found in 12 of 22 cases, 5 of which were diagnosed as bloody turbidity. Premature rupture of the membranes was found in 7 of 22 cases (Table 2). Placental pathology revealed CAM in all cases. Funisitis was found in 17 of 22 cases and not at all in 5 cases. CAM stage/funisitis stage were as follows: stage III/stage III in 8 cases, stage III/stage II in 1 case, stage III/stage I in 1 case, stage III/stage 0 in 2 cases, stage II/stage III in 4 cases, stage II/stage II in 2 cases, stage II/stage 0 in 1 case, stage I/stage I in 1 case, and stage I/stage 0 in 2 cases. The APR-Sc score was 0 in 18 cases, 2 or 3 points corresponding to the acute phase in 0 cases, 2 points corresponding to the subacute phase with elevated AGP and Hp in 2 cases, elevated AGP only in 1 case, and elevated Hp only in 1 case in the convalescent or healing phase .Cord blood IgM was measured in 20 cases, and 8 cases had elevations of 30 mg/dL or more, whereas the remaining 12 cases had no elevations.

Discussion

Half a century has already passed since the first report of WMS. In Japan, WMS is now classified as CLD28 type III (confirmed) and type IV (suspected)3). The etiology of WMS is that of an intrauterine infection triggering an inflammatory reaction that spreads to the immature lungs, resulting in respiratory compromise due to spontaneous breathing after birth, and a bubbly lung appearance on chest X-ray. sTo elucidate the pathogenesis of WMS, we have already reported the following results.

1. IL-8 and granulocyte elastase α1 protease inhibitor complex are significantly increased in tracheal aspirates in the early neonatal period, and IL-8 attracts neutrophils in the bloodstream to the lungs as a chemotactic factor, causing lung injury. This is a very common cause of pulmonary injury [10].
2. WMS occurs at a high rate in very low birth weight infants who have leukemoid reaction in the early stages of life [11].
3. Soluble L-selectin in cord blood is significantly increased [12].

4. The development of WMS can be predicted by the degree of increase in the number of neutrophils in airway aspirate in the early postnatal period [13].

The best postnatal respiratory management is high frequency oscillation (HFO) mode ventilation, which temporarily deprives the infant of spontaneous breathing, prevents collapsed lungs with constant positive pressure, and allows normal gas exchange [14]. With the rapid development of neonatal medicine, the original clinical appearance of WMS has been changed. The typical case is the extremely preterm infant who is spared intubation on the first day of life, but whose respiratory compromise gradually worsens to the point that ventilatory therapy is required [1]. However, now that it is becoming more common to save the lives of extremely preterm infants born at 22- or 23-weeks' gestation, we believe that when an extremely preterm infant is born and diagnosed as not having RDS, the fetus was exposed to some stressful inflammatory reaction during the prenatal period, resulting in hypercytokinemia, or fetal inflammatory response syndrome. Inflammatory cytokines stimulate pituitary corticotropin releasing hormone, which in turn stimulates the secretion of adrenocorticotropic hormone. The resulting stimulation of cortisol production stimulates surfactant production in type II alveolar cells in the lungs, resulting in an infant who does not develop RDS at birth [9]. Occasionally, a similar course is achieved when maternal dexamethasone is administered, and maternal-to-fetal steroid transfer is achieved.

Placental pathology is diagnosed by visual examination at birth to evaluate the umbilical cord for yellow, green, or brown staining or decreased transparency. The color of the amniotic membrane on the fetal side can be similarly observed and palpated to check for calcification and degree of fragility. However, microscopic diagnosis is essential to determine the presence or absence of inflammatory cell infiltration and the degree of its dissemination. Therefore, it is necessary to prepare histopathological specimens of the placenta and umbilical cord. In general, placental pathology, the excised specimen is fixed in formalin for 8 to 24 hours, then embedded in a paraffin block, sliced thinly with a microtome, pasted on a glass slide, stained, and covered with a cover glass to complete specimen preparation. The specimen is then examined by a pathologist. This process usually takes two to three days. When a preterm baby, especially an extremely preterm baby on respiratory management, has WMS, bubbling of the lungs often occurs between one and two days of age. Waiting for placental pathology to be diagnosed risks progression of the lung lesions. Therefore, in more premature infants, the best test seems to be to predict the development of WMS immediately after birth.

In diagnosing neonatal infection by APR-Sc, we previously reported that measurements of inflammatory cytokines that promote the production of APRs is preferable for deciding whether to initiate treatment, whereas the APR-Sc is superior for deciding when to terminate treatment [5]. The focus of this study was to determine the timing of infection and inflammation in the infant, as shown in Figure 1, by measuring the changes in APRs and APR-Sc over time and the APRs that were positive. The majority of placental pathology findings in WMS were subacute or convalescent findings, well past the acute stage. The results of this study showed that the majority of patients (81.8%) had an APR-Sc score of 0 at birth (18 cases), which indicates that the inflammation had resolved by the time of birth. This suggests that somewhere during the fetal period, the patient was in an acute phase of infection. Among the remaining four cases with an APR-Sc of 2 or 1, none were in the acute phase, and two cases each were in the subacute and recovery phases. These cases were also observed at birth after the acute phase of infection had passed in the fetal period.

Another notable point is that none of the patients with WMS had a high inflammatory response immediately before birth, i.e., an acute inflammatory response (APR-Sc 3 points or APR-Sc 2 points with CPR and AGP both positive). The acute phase of inflammation may require a certain period of acute, subacute, and convalescent inflammation during the premature lung period of preterm birth to develop WMS. However, the results of this study were based on a small number of subjects (22 cases in total at two institutions), and more studies at a larger number of institutions are needed. In the case of preterm infants, especially very preterm infants, in whom early exacerbation of respiratory failure is often observed, if the APR-Sc score in cord blood or early postnatal infant blood is 0, despite clear signs of intrauterine infection, the lung injury has already occurred in utero and the damage to the immature lung tissue must be significant. Therefore, rather than forcing an infant to breathe spontaneously, it may be possible to improve the infant prognosis by using HFO in a respiratory management mode that can eliminate spontaneous breathing until some degree of lung tissue repair is achieved [14].

Conclusion

When preterm infants, especially very preterm infants, are born to mothers with intrauterine infection, placental pathology should be submitted as soon as possible, and an APR-Sc should be determined from cord blood or early postnatal infant blood. The score can be used to estimate the timing of the infection (inflammation) (acute, subacute, and recovery/healing phases). The APR-Sc may help in the diagnosis of WMS soon after birth.

References

1. Wilson MG, Mikity VG (1960) A new form of respiratory disease in premature infants. AMA J Dis Child 99: 489-499.
2. Northway WH, Rosan RC, Porter D (1967) Pulmonary disease following respirator therapy of hyaline membrane disease-bronchopulmonary dysplasia. N Engl J Med 276: 357-368.
3. Ogawa Y, Takasaki J, Itakura Y, Shimizu H (1997) Epidemiology and classification of chronic lung disease. Pediatr Pulmonol Supp 16: 25-26.

4. Namba F, Fujimura M, Tamura M (2016) Bubbly and cystic appearance in chronic lung disease: Is this diagnosed as Wilson-Mikity syndrome? Pediatr Int 58: 251-253.

5. Nakamura T, Hatanaka D, Yoshioka T, Yamada S, Goto H (2015) Study on the usefulness of APR scores from the viewpoint of proinflammatory cytokines. Dis Markers Na2015: 981981.

6. Amy Hoepker, Michael Seear, Argyri Petrocheilou, Don Hayes Jr, Arun Nair, et al. (2008) Wilson-Mikity syndrome: Updated diagnostic criteria based on nine cases and a review of the literature. Pediatr Pulmonol 43: 1004-1012.

7. Masato Ito, Seiichi Tomotaki, Tetsuya Isayama, Hiroko Hara, Katsuya Hirata, et al. (2022) The status of chronic lung disease diagnosis in Japan: Secondary publication. Pediatr Int 64: e15184.

8. Blanc WA (1981) Pathology of the placenta, membranes and umbilical cord in bacterial, fungal and viral infections in man. Perinatal Diseases (Naeye R, Kissane J, Kaufman N. eds.), International Academy of Pathology Monograph, Wiliams and Wolkins, Baltimore, London: 5-22.

9. Nakayama M (2003) Placental pathology of intrauterine infection. Arch Histopathol 10: 1-5.

10. Takasaki J, Ogawa Y (1996) Interleukin 8 and granulocyte elastase alpha 1 protease inhibitor complex in the tracheobronchial aspirate of infants with chronic lung disease following inter-uterine infection. Acta Paediatr Jpn 38: 132-136.

11. T Nakamura, S Ezaki, J Takasaki, K Itabashi, Y Ogawa (2002) Leukemoid reaction and chronic lung disease in infants with very low birth weight. J Matern Fetal Neonatal Med 11: 396-399.

12. Nakamura T (2020) The mechanism of onset in neonatal leukemoid reaction: Synergistic effect of proinflammatory cytokines including interleukin 6. Advances in Medicine and Biology (Berhardt LV ed) Nova Science Publishers, Inc. New York 165: 49-97.

13. Nakamura T, Itakura Y, Itabashi K, Ogawa Y (2003) Very early post-natal prediction of type Ⅱ, Ⅱ' chronic lung disease by the combination of tracheal aspirate and peripheral blood cytology. J Jpn Soc Premature Newborn Med (in Japanese) 15: 51-56.

14. Ogawa Y, Shimizu H, Takasaki J, Nakamura T (1999) Strategy for the prevention and treatment of chronic lung disease of the premature infant. Pediatr Pulmonol Suppl 18: 212-215.

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