Agranular Platelets as a Cardinal Feature of ARC Syndrome

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Summary: We aimed to describe abnormal platelet morphology and its clinical significance in infants who were diagnosed with arthrogryposis renal dysfunction and cholestasis (ARC) syndrome. We collected all of the cases of ARC syndrome referred to a single pediatric referral center. In all patients, platelet counts and analysis of platelet morphology were performed with peripheral blood smear specimens. Electron microscopy images were obtained to examine the ultrastructure of the platelets. Over the 12-year period, 12 cases of ARC syndrome were identified. The sex ratio (male:female) was 1:1. The median birth weight was 3.15 kg (range, 2.3 to 3.8 kg). Failure to thrive was observed in all the patients. The major cause of death was recurrent febrile illness and pneumonia. The median age at death was 8.9 months (range, 2.6 to 28.8 kg). Their median body weight at death was 3.1 kg (range, 2.6 to 6.0 kg). Close examination of their peripheral blood smear ($n = 11$) specimens showed large, pale, agranular platelets similar to those seen in gray platelet syndrome. Electron microscopic images of the platelets ($n = 7$) revealed a lack of α; granules. Agranular platelets are a common finding in ARC syndrome. Agranular platelets should be considered as a cardinal feature of ARC syndrome and can be useful as a noninvasive diagnostic marker for ARC syndrome.

Key Words: ARC syndrome, cholestasis, α granule, gray platelet, VPS 33B

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Since the first report of arthrogryposis renal dysfunction and cholestasis (ARC) syndrome (OMIM 208085) by Lutz-Richner and Landolt in 1973,[1] this very rare and lethal infantile disease has been reported worldwide.[2–11] ARC syndrome has 3 cardinal clinical features: arthrogryposis, renal tubular acidosis, and cholestasis with low-serum gamma-glutamyl transpeptidase (γ-GT) activity. In addition, ichthyosis[3,4,12] and failure to thrive[5,6] have been found in most, if not all, patients earlier. There exist other phenotypic features such as nephrogenic diabetes insipidus,[5,13] cerebral malformations,[5,11] sensorineural hearing loss,[11] recurrent febrile illness,[6,11] and dysmorphic features.[3,13] As more patients with ARC syndrome have been identified, it has become apparent that patients with ARC syndrome occasionally present with excessive bleeding after invasive procedure such as organ biopsy of liver or kidney, which may be associated with morbidity and mortality.[3–6,8,14] In addition, there have been several case reports showing clinical presentations suggestive of spontaneous bleeding in these patients.[3,5] In 2 earlier reports of ARC syndrome,[3,6] morphologic studies of platelets revealed abnormal platelets similar to those found in gray platelet syndrome (GPS) and characterized by a severe reduction in α granule number and contents. However, this platelet abnormality was not identified as a cardinal phenotypic feature of ARC syndrome in earlier reports. In this study, we described the clinical features of patients diagnosed clinically with ARC syndrome with special reference to the abnormal platelet. We could identify morphologic features of α granule deficiency in all our patients and suggest that this characteristic can be identified in most, if not all, patients with ARC.

MATERIALS AND METHODS

We collected all the cases of ARC syndrome that were referred to Severance Children's Hospital in Korea over a 12-year period beginning in January 1997 to April 2009. Clinical features and data from the results of investigations were obtained from medical records. A clinical diagnosis of ARC syndrome was based on 3 cardinal clinical features of arthrogryposis, renal tubular dysfunction, and cholestasis with a low-serum γ-GT activity. In all patients, platelet counts and analysis of platelet morphology were prospectively performed with peripheral blood smear (PBS) specimens. Electron microscopy (EM) images were obtained to examine the ultrastructure of the platelets. Briefly, blood was anticoagulated with sodium citrate and platelet-rich plasma was obtained by centrifugation at 200*g* for 20 minutes. One milliliter of platelet-rich plasma was mixed with same volume of Karnovsky fixative (2% glutaraldehyde, 2% paraformaldehyde, 0.5% $CaCl_2$ in 0.1 M phosphate-buffered saline, pH 7.4) and incubated for 6 hours. After washing once with 0.1 M phosphate-buffered saline, the pellet was suspended in 1% OsO_4 (0.1 M phosphate-buffered saline) for the second fixation for 2 hours. After fixation, the platelets were dehydrated by increasing the concentration of alcohol, which was then replaced with propylene oxide. The platelet suspension was embedded in the same volume of EPON mixture. The optimal area in the 0.25 μm section, selected by light microscope, was thin sectioned (80 nm), mounted on a copper grid, and double stained with uranyl acetate and lead citrate. Study protocols were reviewed and approved by the Yonsei University College of Medicine Research Ethics Committee.

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RESULTS

Relative Incidence of ARC Syndrome Among Patients With Neonatal Jaundice

During the study period, a total of 380 patients were admitted due to a diagnosis of neonatal jaundice. Underlying causes of neonatal jaundice included biliary atresia in 137 patients (36%), neonatal hepatitis in 103 patients (27%), choledochal cyst in 38 patients (10%), Allagile syndrome in 15 patients (4%), ARC syndrome in 12 patients (3%), and other cholestasis in 75 patients (20%). Relative incidence of ARC syndrome relative to biliary atresia was 12:137 (1:11.4) (Fig. 1).

Clinical Features of the Patients With ARC Syndrome

Clinical features from the 12 patients with ARC syndrome are shown in Table 1. There was 1 case of familial occurrence (siblings) and 1 case of parental consanguinity (same family lineage in Korea) among the patients. There were 6 male and 6 female patients with the sex ratio being equal. In 9 patients, prenatal ultrasonography was normal. For 3 patients, prenatal diagnosis was possible (2 oligohydroamniosis and 1 arthrogryposis). All patients were born by c-section due to breech delivery with median gestational age of 38.9 weeks (range, 35.3 to 40.4 wk). The median birth weight was 3.15 kg (range, 2.3 to 3.8 kg). All 12 patients presented arthrogryposis with multiple contractures of their joints. Four patients showed congenital dislocation of the hip. One patient showed rickets and bilateral femur fractures. Ten patients showed renal tubular dysfunction. Among them, 2 patients showed nephrogenic diabetes insipidus that was treated with bicarbonate, thiazide, and fluid replacement. One suffered from acute renal failure requiring acute peritoneal dialysis (PD). After PD catheter insertion, he bled at the PD catheter site. All 12 patients presented neonatal jaundice with laboratory finding of conjugated hyperbilirubinemia. However, their serum γ-GT levels were within normal range. Liver biopsy was performed in 5 patients including 2 patients who underwent Kasai portoenterostomy (in 1 patient, operative cholangiography revealed findings compatible with type 2 extrahepatic biliary atresia. In the other patient, portoenterostomy was performed with palliative aim of improving the severe, progressive conjugated hyperbilirubinemia). The major histopathologic findings were "paucity of the intrahepatic bile duct" without ductular proliferation. All patients showed skin ichthyosis from birth except 1 patient who showed marked laxity of skin over the abdomen and extremities, but skin biopsy showed no evidence of ichthyosis. Eight patients underwent radiologic evaluation of central nervous system (neurosonography or brain magnetic resonance imaging), which revealed that 7 patients had a defect in the corpus callosum (agenesis or dysgenesis). Failure to thrive was observed in all 12 patients with poor oral intake, poor motor activity, and poor weight gain. The major cause of death was recurrent febrile illness and pneumonia. At the time this study was written, 9 patients had died and 3 were alive. The median age at death in 9 patients was 8.9 months (range, 2.6 to 28.8 mo) with their median body weight at death of 3.1 kg (range, 2.6 to 6.0 kg).

Clinical Features and Morphologic Study of Platelet in Patients With ARC Syndrome

One patient (patient 3) who underwent Kasai portoenterostomy presented postoperative bleeding requiring multiple transfusions. Platelet aggregation study of the patient was abnormal in response to adenosine diphosphate and collagen. One patient (patient 5) was noted to have frequent epistaxis and melena. One patient (patient 6) suffered from acute renal failure and required acute PD. After PD catheter insertion, he bled at the PD catheter site requiring multiple repair procedures. The median platelet count of the 12 patients was 367 k (range, 256 to 463 k) (Table 2). Except the first case in whom PBS was not carefully examined, all 11 patients showed abnormally large, pale, and agranular platelets in the PBS specimen (Fig. 2). EM study was available in the 7 patients, which showed that most platelets virtually lacked recognizable α granules. Only empty vacuoles as the remnants of α granules that have lost their granular contents were observed. No notable abnormality was found in other organelles such as mitochondria and δ granules (Fig. 3).

DISCUSSION

In this study, we have presented 12 cases of ARC syndrome diagnosed at a major referral center for the treatment of neonatal jaundice (Severance Pediatric Liver Disease Research Group). In all cases, abnormal platelet morphology was noted (Table 2). All cases with 1 exception of patient 1, in whom a PBS was not performed, had large, pale, and agranular platelets that can be seen in GPS.

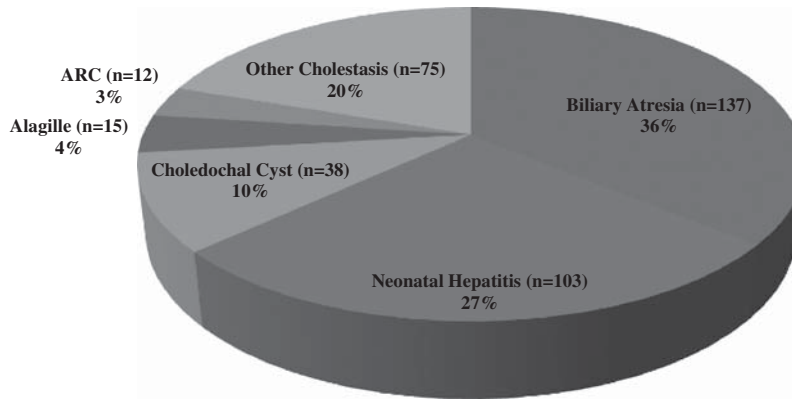

FIGURE 1. Underlying causes of neonatal cholestasis in 380 infants at the Yonsei University Health System (January 1997 to April 2009)

TABLE 1. Clinical Features of Patients Presented in the Study

Case Number	1	2	3	4	5	6	7*	8	9	10†	11‡	12
Sex	F	F	M	M	F	M	M	M	F	F	M	F
Birth weight (kg)	2.7	3.2	3.4	3.3	3.2	2.5	3.1	3.1	3.2	2.3	2.7	3.8
Arthrogryposis	+§	+	+§	+	+§	+	+	+	+	+	+§	+
RTA	+	+	+	−‖	+¶	+¶#	+	+	+	+	+	−‖
Cholestasis	+	+**	+**	+	+	+	+	+	+	+	+	+
SGOT (IU/L)	28	35	41	27	132	57	128	42	57	39	50	28
SGPT (IU/L)	22	15	31	17	119	40	7	36	56	15	56	40
T.bil (mg/dL)	11.7	13.8	9.2	8.3	16.2	9.1	7.2	9.2	11.8	8.9	12.8	3.7
D.bil (mg/dL)	7.8	10.2	6.4	6.9	12.4	7.0	1.8	7.5	11.2	7.2	10.5	3.2
γ-GT (IU/L)	ND	ND	29	24	23	19	30	15	24	14	33	43
Bile duct paucity	+	+	+	+	ND	ND	ND	ND	ND	ND	ND	+
Ichthyosis	+	+	+	+	+	+	−	+	+	+	+	+
CNS anomaly	ND	+	+	+	−	+	ND	ND	ND	+	+	+
Failure to thrive	+	+	+	+	+	+	+	+	+	+	+	+
Age (mo) at death	4.1	26.7	8.9	4.9	28.8	11.5	5.3	2.6	11.8	Alive	Alive	Alive
Body weight (kg) at death	3.3	2.7	3.8	NK	6.0	2.8	2.9	3.2	2.6	2.7††	3.5††	3.5††

*Second child of an unrelated Korean couple and the sibling of the patient described in patient 3.
†She was the child of healthy parents with the same family lineage.
‡Congenital hypothyroidism was diagnosed, and levothyroxine replacement therapy was started.
§Four patients showed congenital dislocation of the hip.
‖]Two patients had no clinical findings of renal tubular acidosis except for transient proteinuria and glycosuria.
¶The patient also had renal tubular acidosis and nephrogenic diabetes insipidus that was treated with bicarbonate, thiazide, and fluid replacement.
#The patient suffered from acute renal failure and required acute peritoneal dialysis.
**Two patients underwent Kasai portoenterostomy under diagnosis of biliary atresia.
††At the time this study was written, patient 10 was alive and 20.9 months old with a weight of 2.7 kg at last follow-up, patient 11 was alive and 3.3 months old, and patient 12 was alive and 4.3 months old with a weight of 3.5 kg.
††Body weight at last follow-up.
CNS indicates central nervous system; D.bil, direct bilirubin; F, female; γ-GT, gamma glutamyl transpeptidase; M, male; ND, not done; NK, not known; RTA, renal tubular acidosis; SGOT, serum glumatic oxaloacetic transaminase; SGPT, serum glumatic pyruvic transaminase; T.bil, total bilirubin.

This finding emphasizes that the identification of agranular platelets support the diagnosis of ARC syndrome in patients who have all other features of ARC. These findings also explain the platelet dysfunction seen in these patients, risking severe bleeding with invasive procedures. In fact, patient 2 in this study had very similar clinical features to the patients reported by Deal et al[3] wherein the patients had renal tubular acidosis, ichthyosis, dysmorphisms, and jaundice. At the time the initial study was written, few cases of ARC syndrome had been reported. (In fact the clinical features described by Deal et al were those of a classic ARC syndrome for which an acronym was given to the condition in 1994.[13]) Deal et al described abnormal platelet morphology with EM imaging and remarked that these patients represented the ''the first report of abnormal platelet morphology with Fanconi syndrome.'' This report prompted us to perform a platelet morphology study in all the patients as patient 2 was suspected to have ARC syndrome. Thus, we prospectively performed the study of platelet morphology by PBS and EM in this patient population. Review of the literature with regard to ARC syndrome has failed to reveal the importance of abnormally large, agranular platelets on PBS as a diagnostic marker for ARC syndrome. Most studies are focused on the fact that gray platelets are an additional incidental clinical finding in ARC patients. We were surprised that all the 11 patients who were being worked up for ARC syndrome had abnormal platelet morphology with relatively large, agranular, and pale-appearing platelets at least on light microscopy. For all the 7 patients for whose EM findings were available (4 patients did not provide consent for EM imaging), the EM images showed platelets with vacuolar change, a lack of α granules, and intact δ granules and mitochondria. Thus, these data provide evidence that agranular platelets may be a diagnostic marker in ARC syndrome. Recently, it has become clear that these abnormal platelets are a common finding that can be seen in patients with ARC syndrome.[12,15,16] Earlier studies have already provided

TABLE 2. Clinical Features Suggesting a Bleeding Tendency and Morphologic Study of Platelet in ARC Syndrome

Case Number	1	2	3	4	5	6	7	8	9	10	11	12
Bleeding tendency	−	−	+*	−	+†	+‡	−	−	−	−	−	−
Platelet count (k)	463	450	301	427	266	256	348	421	293	382	351	401
Agranular platelet		+	+	+	+	+	+	+	+	+	+	+
LM	ND	+	+	+	+	+	+	+	+	+	+	+
EM	ND	+	+	+	+	ND	ND	ND	ND	+	+	+

*Postoperative bleeding requiring multiple transfusions. A platelet aggregation study was abnormal in response to adenosine diphosphate (ADP) and collagen.
†During inpatient course, the patient was noted to have frequent epistaxis and melena.
‡The patient suffered from acute renal failure and required acute peritoneal dialysis (PD). After PD catheter insertion, he bled at the PD catheter site.
ARC indicates arthrogryposis renal dysfunction and cholestasis; EM, electron microscopy; LM, light microscopy.

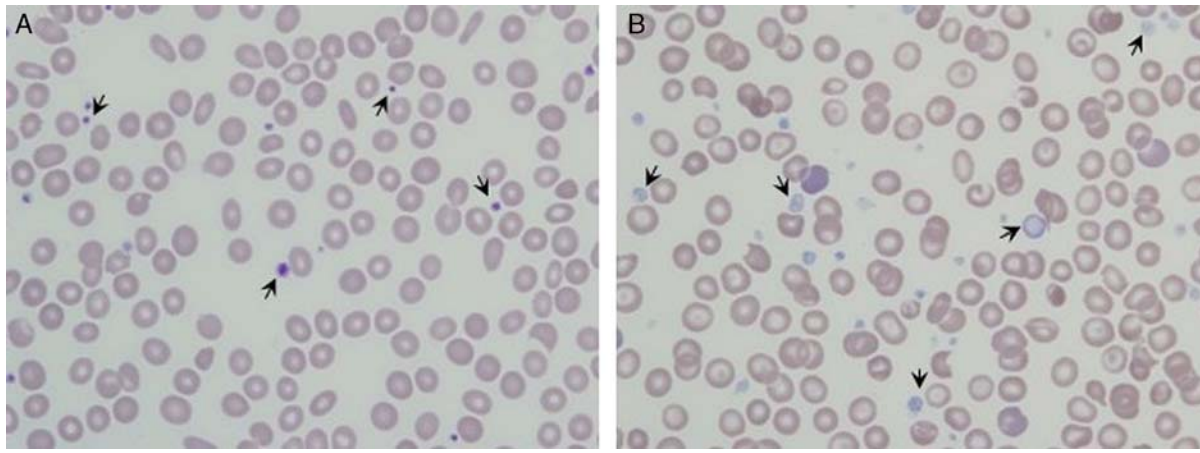

FIGURE 2. A, Light microscopy of platelets of a normal neonate as the control (arrows) that are typically small, granular, and stained dark blue. Azurophilic granulles tend to concentrate in the center of the cell. B, Platelets in patient with ARC syndrome (patient 2). Note that most platelets (arrows) are relatively large and pale due to lack of normal granulation compared with control (peripheral blood smear, Wright-Giemsa stain, original magnification: $\times$ 400). ARC indicates arthrogryposis renal dysfunction and cholestasis.

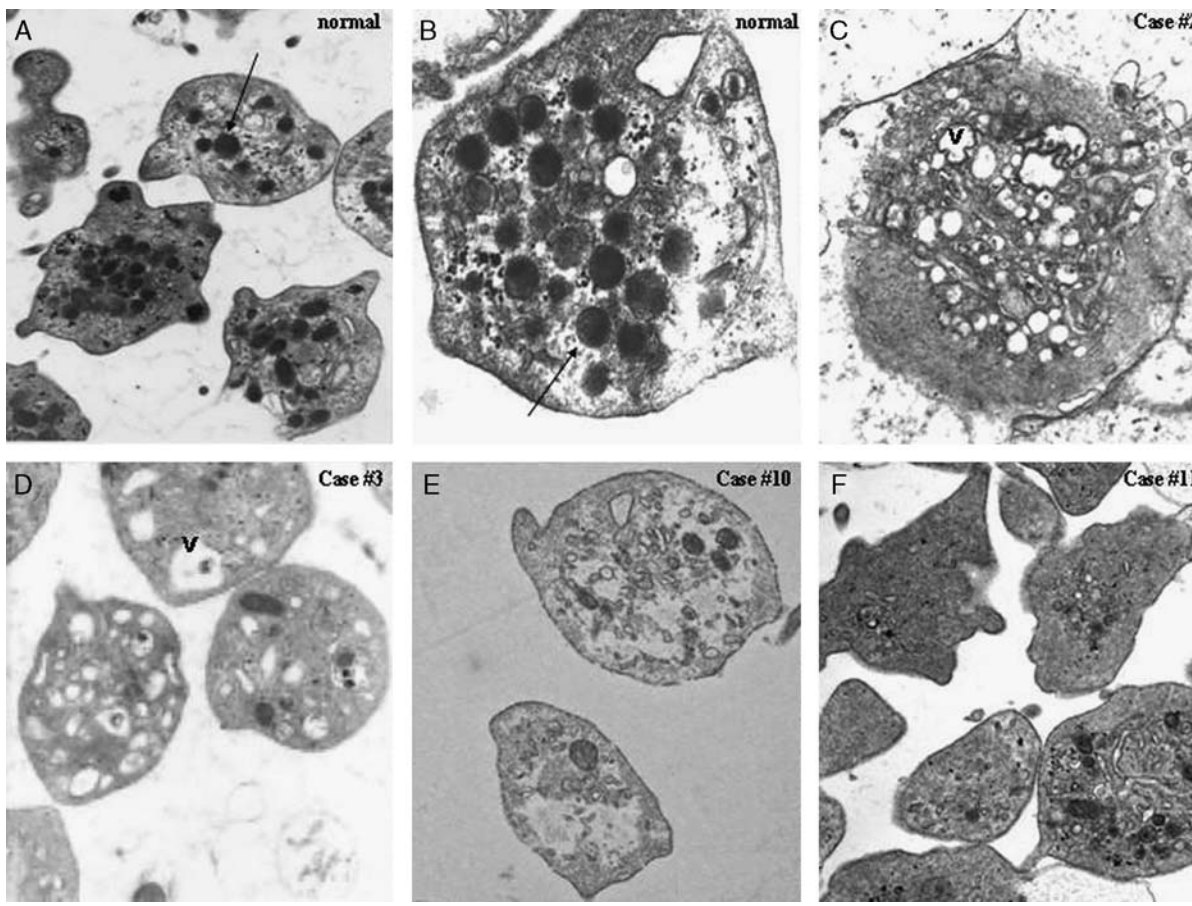

FIGURE 3. Representative findings of electron microscopy images in normal neonatal platelets (A, B) and platelets in patients with ARC syndrome [(C): case 2, (D): case 3, (E): case 10, (F): case 11]. Magnifications are $\times$ 11,500 (A), $\times$ 28,500 (B), $\times$ 21,000 (C), and $\times$ 20,000 (D to F). Normal platelets have abundant electron-dense á granules (arrow). In contrast, most platelets seen in ARC syndrome virtually lack recognizable α granules. Only empty vacuoles (v) as the remnants of α granules that have lost their granular contents are observed (C, D). There are also hypogranular platelets in patients with ARC syndrome (E, F). No notable abnormalities are found in other organelles such as mitochondria and δ granules. ARC indicates arthrogryposis renal dysfunction and cholestasis.

TABLE 3. Published Reports of Individual Patients With ARC Syndrome Who Presented With Acute Bleeding and the Clinical Consequences

	No. Cases*	Pertinent Case	Clinical Consequences
	6 (6)	Patient 3	Hemoperitoneum after liver biopsy
	6 (6)	Patient 5	Bleeding after renal biopsy
	5 (4)	Patient 4	Died from hemorrhage following a liver biopsy
	4 (5)	Patient 1	Cerebral bleeding
	6 (3)	Patient 4, 5	Gastrointestinal bleeding
	1 (8)	Patient 1	Hemoperitoneum after liver biopsy
	1 (17)	Patient 1	Hemoperitoneum after portoenterostomy
Total	23	8	

*Numbers in square brackets denote reference numbers.
ARC indicates arthrogryposis renal dysfunction and cholestasis.

evidence that patients with ARC syndrome have an increased likelihood of hemorrhage that may lead to morbidity and mortality. This increased likelihood of hemorrhage in ARC syndrome is thought to be associated with a defect in platelet α granules. In reviewing the literature, including that of patient 3, of the patients who underwent Kasai portoenterostomy, a total of 8 of 23 patients with ARC syndrome had an acute and fatal hemorrhage (Table 3). Five patients had excessive bleeding after liver[4,6,8,17] and renal biopsies.[6] Three patients had spontaneous cerebral[5] and gastrointestinal bleeding.[3] In addition, patient 5 had frequent epistaxis and gastrointestinal bleeding, and patient 6 had excessive bleeding at the insertion site of PD catheter and required multiple repair procedures. Unfortunately, few patients with ARC syndrome in whom platelet morphology was studied have been reported. Of all those patients with ARC syndrome in whom platelet morphology was studied, agranular platelets have been noted (Table 4). As far as platelet function in ARC syndrome is concerned, we have reported earlier only 1 patient (patient 3) who had abnormally large and pale platelets without a secondary aggregation wave with collagen and adenosine diphosphate and with a normal response to epinephrine and mildly decreased response to ristocetin.[17] von Willebrand factor and p-selectin (an α granule membrane protein) plasma markers were markedly increased, although they were nearly

TABLE 4. Published Reports of Individual Patients With ARC Syndrome in Whom Platelet Morphology was Studied

	No. Cases*	Pertinent Case	Study Findings
	6 (6)	Patients 3, 4, 5, 6	Abnormally large, pale, agranular platelets on LM
	6 (3)	Patients 2, 6	Agranular platelets (no α granules) on EM
	1 (17)	Patient 1	Agranular platelets (no α granules) on EM
Total	13	7†	

*Numbers in square brackets denote reference numbers.
†Platelet morphology was not studied in the other 6 patients in the study.
ARC indicates arthrogryposis renal dysfunction and cholestasis; EM, electron microscopy; LM, light microscopy.

absent within the platelet itself. Agranular platelets in patients with ARC syndrome have several characteristics that are different from the classic GPS described by Raccuglia.[18] First, patients with ARC syndrome do not have thrombocytopenia. All patients in this study had a normal platelet count. This normal finding makes it more difficult for clinicians to be aware of the increased risk of bleeding, especially in those with an incomplete ARC syndrome phenotype. We also speculate that many minor hemorrhage events in patients with ARC syndrome are unnoticed by clinicians. Second, unlike in classic GPS, platelets in patients with ARC syndrome have a complete absence of α granule membrane structure. Two earlier studies have described that in patients with ARC syndrome, p-selectin is only detected in the plasma.[15,17] Considering that patients with ARC syndrome have many congenital anomalies, agranular platelets may be a morphologic indication of a more profound molecular disorder than that found in classic GPS, a platelet storage pool disorder. Recently, it was found that VPS33B, a vacuolar protein sorting gene, located in 15q26.1, is mutated and loses function in ARC syndrome.[19] VPS33B contains a Sec1-like domain and belongs to the family of SM (sec/munc-18 protein) proteins that bind tightly to members of the syntaxin family of target SNAREs (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor). In doing so, VPS33B causes vesicles to target the SNARE complex assembly, which is an essential process for endosomal fusion in the intracellular trafficking of endosomes. Human VPS33B is ubiquitously expressed in fetal and adult tissues.[20] In this regard, various phenotypic anomalies in patients with ARC syndrome are now explained by the VPS33B mutation.[15,19,21] Earlier studies have shown that a loss-of-function mutation in VPS33B results in defective biogenesis of α granules and granular proteins.[15] To our knowledge, this study includes the largest ever series of patients with ARC syndrome who have presented with abnormal platelet morphology and the detailed analysis of platelets performed by interested hematologists. Our results suggest that the observation of agranular platelets on PBS is important for making the diagnosis of ARC syndrome in patients in whom ARC syndrome is suspected. The results of our study have several clinical implications. First, investigation of platelet morphology can be very helpful in diagnosing ARC syndrome. For patients presenting with neonatal jaundice, early diagnosis of ARC syndrome is important because this subset of patients has a poor prognosis and high mortality. Furthermore, early diagnosis is difficult, especially when the other components of ARC syndrome may not be evident. Second, the presence of abnormal platelets has a high sensitivity for making the diagnosis of ARC syndrome. The presence of agranular platelets in patients suspected to have ARC syndrome may add diagnostic accuracy, which is especially pertinent for patients with incomplete ARC syndrome. Third, analysis of platelet morphology should replace organ biopsy as a first-line diagnostic test for patients with features of ARC syndrome. There is some debate about liver biopsy as a diagnostic procedure in ARC patients.[8,22] We strongly agree with Hayes et al[8] that organ biopsy should not be recommended because ARC patients are prone to excessive bleeding after invasive procedures. We conclude that agranular platelets are a common finding in ARC syndrome, so platelet morphology should be carefully examined in all infants who are suspected of having ARC

syndrome. We suggest that agranular platelets should be considered as a cardinal feature of ARC syndrome and can be useful as a noninvasive diagnostic marker for ARC syndrome. As this is a rare disorder, agranular platelet on PBS has an importance that raises physicians' awareness and would help to improve the diagnosis and outcome of those patients. Invasive procedure such as organ biopsy that may cause bleeding should be avoided, if possible, in patients suspected of having ARC syndrome.

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