

## Good outcomes in operative management of acquired prothrombin complex deficiency: a serial case report

Lola Purnama Dewi,<sup>1</sup> Eka Nurfitri,<sup>1</sup> Evodia,<sup>2</sup> M. Tiya Romli<sup>2</sup>

### Abstract

**Background** Acquired prothrombin complex deficiency (APCD) is a serious bleeding disorder in infants caused by idiopathic vitamin K deficiency. This disorder has a high mortality rate and sequelae are often seen in those that survive. The principal treatments are giving vitamin K and evacuating hemorrhages.

**Objective** To report the outcome of surgical and non-surgical management in several cases of APCD.

**Method** Eighteen infants diagnosed with APCD had similar histories: all were less than 4 months of age as well as exclusively breastfed, and none received vitamin K injections after birth. The diagnosis of APCD was made based on prolonged prothrombin times and proven intracranial hemorrhage on brain CT-scan. All subjects were treated with vitamin K injections for 5 days and offered craniotomy procedures.

**Results** Out of 18 subjects, 10 underwent craniotomies, 9 within 48 hours of diagnosis and 1 on the fifth day of hospitalization. Two patients with small subdural hematomas were treated conservatively. Four subjects refused hospitalization. Two refused the craniotomy and died. All patients treated (12 cases), with both surgical and conservative treatment, were survived. Survivors were followed for 6 months and 10 of whom returned to the hospital for follow-up (9 patients who had operative procedures and 1 who did not). One patient who with craniotomy on the fifth day hospitalization had hydrocephalus as a sequela.

**Conclusion** Operative procedure was needed for treatment of APCD in some cases with moderate until severe intracranial bleeding, while vitamin K injection only stop the progress of intracranial bleeding not as curable treatment of massive intracranial bleeding. [Paediatr Indones. 2011;51:298-302].

**Keywords:** APCD, Vitamin K, craniotomy, mortality

Intracranial hemorrhage (ICH) due to idiopathic vitamin K deficiency (VKD) or acquired prothrombin complex deficiency (APCD) is still a problem even in the era of vitamin K prophylaxis.<sup>1,2</sup> It is a serious bleeding disorder in the early infantile period that has a high mortality rate and may cause permanent neurological sequelae in survivors.<sup>1-7</sup>

The majority of cases reported in literature occurred in Japan and Thailand. The incidence of APCD in Thailand was 35.5 per 100,000 live births in 1966, making this disorder a public health problem for the nation. Data suggest that low vitamin K intake by infants is responsible for the disorders, however, some patients given vitamin K prophylactically at birth still suffered this syndrome.<sup>1</sup> Breast milk was found to have lower level of vitamin K than formula milk, thus breastfed infants had a higher risk of APCD syndrome.<sup>1,8</sup> Moreover, to reduce APCD incidence, mass vitamin K injections are mandatory for newborns in the first 6 hours of life in Indonesia.

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From the Department of Child Health, Fatmawati Hospital, Jakarta, Indonesia.<sup>1</sup> From the Department of Neurosurgery, Fatmawati Hospital, Jakarta, Indonesia.<sup>2</sup>

**Reprint requests to:** Lola Purnama Dewi, MD, Department of Child Health, Fatmawati Hospital, Jakarta, Indonesia. E-mail: lolapurnama\_dewi@hotmail.com

Conservative treatment of ICH due to APCD is sometimes insufficient and depends on the size of ICH. Therefore, we conducted a case report study in infants with ICH due to APCD who were admitted to Pediatric Intensive Care Unit of Fatmawati Hospital.

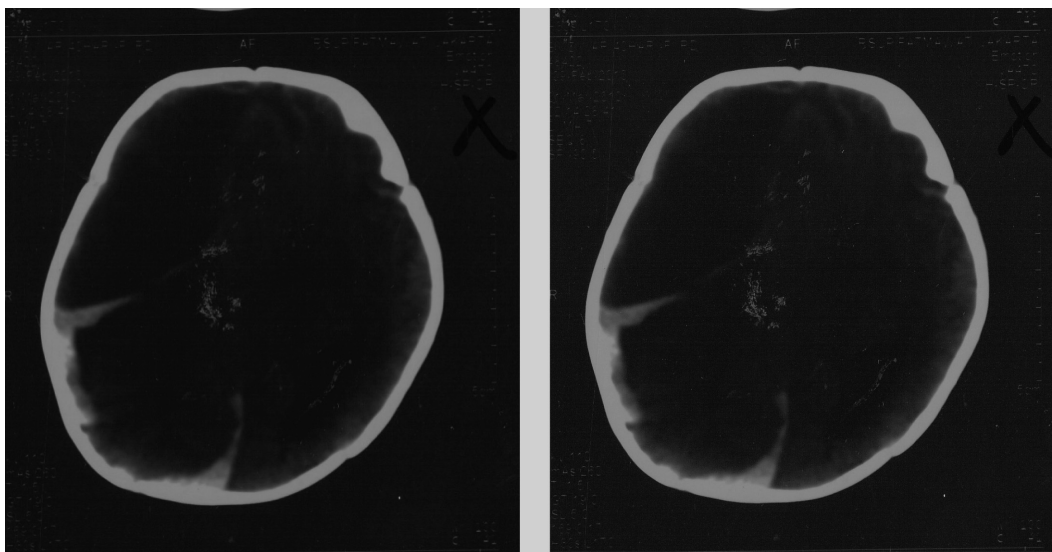
## Methods

Eighteen exclusively breastfed infants, aged 2 weeks to 4 months with decreased consciousness, and suspected omission of vitamin K injection after birth were diagnosed with APCD. This diagnosis was made based on prolonged prothrombin time (PT), abnormal partial thromboplastin time (PTT), normal platelet count, and proven intracranial hemorrhage by brain CT-scan. We excluded subjects with liver impairment, severe malnutrition, sepsis, and those receiving antibiotics in the last seven days. Information was obtained to identify risk factors of APCD including form of feeding, vitamin K prophylaxis, labour assistance, nutritional status, drug consumption, history of blood transfusions, and sepsis during the neonatal period.

All subjects were treated with vitamin K injection for 5 days and offered craniotomies to relieve massive intracranial hemorrhages observed by brain CT-scan.

## Results

We reviewed the cases of 18 patients with intracranial hemorrhage due to acquired prothrombin complex deficiency. Clinical manifestations included deterioration of consciousness, bulging anterior fontanelle, pallor, mild hepatomegaly, mild fever, and no other associated hemorrhage sites. By history, all patients were exclusively breastfed, and 16 were born assisted by a traditional midwife (*paraji*), while 2 patients were born assisted by a midwife. We assumed that none of the patients who were assisted by traditional midwives received injected or oral vitamin K. We were uncertain if vitamin K was administered to the 2 patients born assisted by midwife, because their parents were uninformed on the matter. The mean age of the patients was 10 weeks, and there was no difference in gender distribution (9 males vs 9 females). Four subjects refused hospitalization.



**Figure 1.** Moderate subdural hemorrhage: the patient was a 10 week-old boy whose delivery was assisted by traditional midwife. He had no history of vitamin K injection and was exclusively breastfed. Upon presentation he was stuporous with bulging fontanelles, severe anemia, lengthened prothrombin time, normal liver function and no other signs of hemorrhage.

We classified intracranial hemorrhages into 3 groups based on radiologic findings: small (less than 3 cm), medium (3-6 cm), and large (more than 6 cm). Nine patients underwent craniotomy within 48 hours, one of whom was on a ventilator before the surgery. One patient underwent craniotomy on the fifth day of hospitalization, following lack of improvement by mechanical ventilation and other non-operative treatment. All patients who underwent craniotomy had medium-large hemorrhage (Figure 1) and were survived. Two cases were treated conservatively due to their small subdural hemorrhage; they received only vitamin K injections and fresh frozen plasma. One patient with a moderate subdural hematoma and one patient with a large subdural hematoma refused the craniotomy. They were put on ventilators with a target pCO<sub>2</sub> of less than 35 mmHg, and given mannitol, fresh frozen plasma and vitamin K. Both died on the second day of pediatric intensive care unit stay.

## Discussion

Vitamin K is an essential, fat-soluble vitamin that is required for the post-translational gamma carboxylation of the coagulation factors II, VII, IX, X, and proteins C and S. These factors contain the unique amino acid, gamma-carboxyglutamic acid, which is necessary for calcium-binding and essential for coagulation function.<sup>10</sup> Hemorrhagic disease in newborns resulting from severe transient deficiencies in Vitamin K-dependent factors is characterized by bleeding that tends to be gastrointestinal, nasal, subgaleal, intracranial or postcircumcision. An acute onset, short course, and high rate of intracranial bleeding is found in 65% cases of hemorrhagic diseases due to vitamin K deficiency.<sup>4,5</sup> Prodromal or warning signs (mild bleeding) may occur before serious intracranial hemorrhage.<sup>1,6</sup> Intracranial hemorrhages have been reported in the subarachnoid space, the parenchyma, and the ventricle.<sup>1</sup> Clinical manifestations of high frequency in VKD consisted of bleeding, pallor and mild hepatomegaly. In addition, mild fever, diarrhoea, jaundice, and upper respiratory tract infection were observed in a few patients. The prothrombin time (PT) was prolonged in all subjects.

The routine use of intramuscular vitamin K for prophylaxis in the United States is believed to be safe and not associated with an increased risk of childhood cancer or leukemia. Although oral vitamin K (dosage of 1–2 mg at birth, discharge, and 3–4 weeks) has been suggested as an alternative, its effectiveness has not been established. Therefore, the intramuscular route remains the method of choice.<sup>6</sup> Since the introduction of this prophylaxis, the incidence of vitamin K deficiency bleeding (VKDB) has decreased, though late VKDB is still reported.<sup>9-11</sup>

Several studies have been reported on APCD in various countries. In 1977, Blanchet *et al.* reported 93 cases with acute bleeding due to acquired prothrombin complex deficiency. The incidence of intracranial bleeding was strikingly high (63%), particularly in the form of subdural and subarachnoid hemorrhage. Acute onset, short course and rapid clinical and laboratory improvement after vitamin K therapy were observed.<sup>10,13</sup> Subsequent attention has been drawn to this disease as a major health problem in infants in Southeast Asia because of its high prevalence (30-80 per 100,000 births) along with the high incidence of intracranial bleeding (80%), high mortality (25%) and permanent neurological handicap (50-65%). In the early 1980s, VKDB was also a major problem in Europe and Japan,<sup>10</sup> with incidences from 1 in 200-400 infants to 0.4-1.7 in 100 infants who did not have vitamin K prophylaxis and were exclusively breastfed.<sup>10,11</sup>

Chaou *et al.* reported late-onset (0.5 to 6 months of age) intracranial hemorrhage related to vitamin K deficiency in 32 breast-fed infants, 31 of whom received no prophylactic vitamin K at birth. Computerized tomography showed mild to severe intracranial hemorrhage. Most (90.6%) had subarachnoid hemorrhages, either by themselves or in combination with subdural hemorrhages (37.5%), parenchymal hemorrhages (31.3%), or intraventricular hemorrhages (12.5%). In remaining subjects (9.4%), the infratentorial region was involved.<sup>16</sup> Of the VKDB-related intracranial hemorrhages reported by Miyasaka *et al.*, brain CT showed hemorrhages in subdural and subarachnoid spaces in six, parenchyma in three, and ventricle in one.<sup>1</sup>

Serious bleeding complications attributed to vitamin K deficiency, such as intracranial bleeding, must be reversed immediately. Despite the rapid action

of vitamin K, its administration should be preceded by an infusion of fresh frozen plasma. This blood component contains all the vitamin K-dependent clotting proteins. In sufficient quantities, fresh frozen plasma can correct, or nearly correct, the PT, as well as the bleeding tendency.<sup>1,6,9,14,17,18</sup>

At present, aggressive surgical management to evacuate clots in patients with acute ICH is not indicated, except in cases of cerebellar ICH. The International Surgical Trial in Intracerebral Hemorrhage (ISTICH) suggested there was no clinical benefit from conventional surgical clot evacuation when compared with conservative medical management in acute ICH. A new clinical trial (STICH 2) is underway to test the hypothesis that minimally invasive surgical evacuation of cortical clots may be beneficial. Patients who have cerebellar ICH with hematomas >40 mL in volume or who have a GCS <14 require early surgical intervention. Neurosurgical consultation for posterior decompression of large cerebellar hematomas should always be considered for patients with cerebellar ICH.<sup>19</sup> Neurosurgical intervention could, however, be lifesaving in a situation in which sudden clinical deterioration is due to a precipitous rise in intracranial pressure. Therefore, it should be seriously considered.<sup>18</sup> Nyquist reported in good outcomes with surgical therapy after spontaneous ICH in children.<sup>19</sup>

Vitamin K deficient hemorrhagic diathesis is well-known as a cause of infantile intracranial hemorrhage. Its occurrence, however, as a post-surgical complication is rare and has never been previously reported.<sup>23</sup> Deng *et al.* reported that 22 infants with intracranial hemorrhage resulting from late-onset vitamin K-deficiency were satisfactorily managed by a minimally-invasive surgical approach for clearance of intracranial hematomas, on the basis of pediatric diagnosis and treatment protocols. Minimally invasive surgery to clear intracranial hematomas may limit the sequelae in the nervous system and reduce the mortality rate of intracranial hemorrhage in infants.<sup>23</sup> Akiyama *et al.* reported that urgent surgical intervention for ICH can be performed successfully following sufficient administration of vitamin K or fresh frozen human plasma in patients with biliary atresia, a condition leading to vitamin K deficiency.<sup>24</sup> Brouwer reported that ICH with

parenchymal involvement carried a risk of adverse neurological sequelae with a mortality rate of 24.5% and development of cerebral palsy (CP) in 8.6%. In spite of frequent, large intraparenchymal lesions, 30 of the 34 survivors without CP (88.2%) had normal neurodevelopmental outcomes at 15 months.<sup>25</sup>

We conclude that intramuscular vitamin K1 prophylaxis should be routinely given to all newborns who will be exclusively breastfed. Operative procedure was needed for treatment of APCD in some cases with moderate until severe intracranial bleeding, while vitamin K injection only stop the progress of intracranial bleeding not as curable treatment of massive intracranial bleeding.

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