Abstract
Acquired Prothrombin Complex Deficiency (APCD) is a condition of where spontaneous bleeding occurs or because of other processes such as venous puncture or an operation due to a decrease in vitamin K dependent coagulation factor activity (factors II, VII, IX dan X). Prevalence of APCD is approximately around 1 per 2 million populations and it does not relate to gender, race, or some certain ethnics. Intracranial bleeding is the most common manifestation of APCD that can be found. Vitamin K deficiency can be caused due to the pathologist condition or can be acquired. Some pathologic conditions that can cause the deficiency of the vitamin K are: liver parenchymal disease, enteropathy or malabsorption syndrome, the reaction of the vitamin E against vitamin K, erythroid multiple myelomadisseminated intravascular coagulopathy, nephrotic syndrome and white blood cells abnormalities. Furthermore, some acquired conditions that cause the deficiency of the vitamin K are: lack of vitamin K intake through food, side effects from various therapies, and overdose on the use of anticoagulants. Evaluation of coagulation factors needs to be done for screening the diagnosis of APCD in the form of isolation of the coagulation pathway and determining deficiency factors or inhibitor factors. Treatment of APCD patients is intended to control bleeding and eliminate inhibitors either with immnosupressive therapy or treatment of the underlying disease. Intake of vitamin K, fresh frozen plasma (FFP), packed red blood cells (PRBC), and prothrombin complex concentrates (PCC) has been shown to reduce morbidity and prevent complications. Intake of prophylactic vitamin K1 in newborns is recommended to prevent APCD.
INTRODUCTION

Acquired Prothrombin Complex Deficiency (APCD) is a condition where spontaneous bleeding occurs or because of other processes such as venous puncture or surgery due to decreased vitamin K dependent coagulation factor activity (factor II, VII, IX and X) while coagulation factor activity is not dependent in vitamin K, such as fibrinogen levels and platelet counts are still within normal limits.1

The prevalence of APCD is around 1 per 2 million populations and does not relate to gender, race or ethnicity. A survey in Japan report the incidence of APCD is 1 per 4,500 infants with 81% of its manifestation is intracranial bleeding. The incidence of PDVK decreases after the prophylactic vitamin K is given in all newborns.2

DEFINITION

Acquired Prothrombin Complex Deficiency (APCD) is a condition where spontaneous bleeding occurs or due to other processes such as vein puncture or surgery which is caused by a decrease in vitamin K dependent coagulation factor activity (factor II, VII, IX and X). The coagulation factor activity that is not dependent on vitamin K, usually fibrinogen levels and platelet counts are still within normal limits.1

Clotting factor II or prothrombin is a proenzyme that is dependent on vitamin K which has a function in the blood coagulation cascade. Factor II deficiency is rare, inherited or acquired disorder with an estimated incidence of one case per 2 million populations.3

According to the US Institute of Medicine the recommended of vitamin K diet is 120 μg in men and 90 μg in women, much lower in other countries and Europe (including Italy) with an average of 1 μg per kg body weight in one day. Vitamin K requirements for pregnant women are no different. The Third National Health and Nutrition Examination Survey set a sufficient threshold for vitamin K intake as 2 μg /kgbw for infants in the first 6 months of life and 2.5 μg /kgbw for infants aged 7-12 months. After this age, adequate intake increases from 30 ug / kgbw in children from 1-3 years, to 75 μg /kgbw in adolescents (up to 18 years).4

ETIOLOGY AND RISK FACTORS

Normal coagulation maintains a balance between pro and antithrombotic mechanisms. Bleeding due to dysfunction of the procoagulant mechanism can be caused by inherited or acquired factors. The most common abnormalities occur due to vitamin K deficiency, warfarin therapy, liver disease, oral anticoagulants, disseminated intravascular coagulation, platelet disorders and vascular disorders. The etiology of this disease is vitamin K deficiency experienced by infants because of: Low levels of vitamin K in the plasma and reserves in the liver, low levels of vitamin K in breast feeding, and no injection of vitamin K1 at birth.1

APCD is a serious bleeding disorder in infants, which causes high mortality rates and permanent neurological sequels, where low vitamin K intake in infants has come up to be the main cause.5 This disease has several possible etiologies. Due to the prothrombin that is synthesized almost exclusively in the liver, severe liver disease has a dramatic impact on the level of prothrombin.6

Vitamin K deficiency can cause a decrease in prothrombin levels. Vitamin K is produced in the intestine by enteric flora, and can be affected by intestinal malabsorption, bile duct obstruction, or antibiotic use.6 Vitamin K deficiency can be induced iatrogenically when the propylthiouracil or vitamin K antagonists; such as warfarin is given. Vitamin K deficiency can also be seen in neonates.7 The most common causes of APCD are severe liver disease, vitamin K deficiency, or administration of vitamin K antagonists (for example, warfarin).8

The cause of APCD associated with pregnancy can come from drugs or from other disorders / diseases. Pregnant women who take drugs that can interfere with vitamin K metabolism; such as oral anticoagulant drugs, anticonvulsants, and antituberculosis drugs. Some disorders such as lack of synthesis of vitamin K by intestinal bacteria, impaired liver function, lack of vitamin K intake can occur in infants who are exclusively breastfed, because breast milk has a low vitamin K content of <20 ug / L when compared to
The cause of vitamin K deficiency


**Picture 1.** Coagulopathy evaluation. The first step: isolating the coagulation pathway. Elongated prothrombin time (PT) indicates a defect in the extrinsic pathway, and elongated activated partial prothrombin time (aPTT) indicates a defect in the intrinsic pathway. When PT and aPTT are prolonged, they indicate defects in both pathways. The second step: determine the deficiency factor or inhibitor factor. If the elongation time is corrected by mixing with normal plasma, then there is a deficiency factor. If the elongation of time cannot be corrected by normal plasma mixing, it means there are inhibitor factors and specific tests must be done.
cow's milk which has 3 times more vitamin K (60 μg/L). In addition, lack of vitamin K intake is also caused by malabsorption syndrome and chronic diarrhea.1

DIAGNOSE

APCD patients usually come and report a family history of bleeding disorders. They can also report a history of symptoms, including: prolonged bleeding after circumcision, postpartum bleeding, easy bruising, bleeding gums, epistaxis, menorrhagia, prolonged bleeding, melena, hematuria, hemarthroses, soft tissue bleeding, and intracranial bleeding.3

Petechiae and/or ecchymosis which usually occur in places with minor trauma can be found in the physical examination. Petechiae or ecchymosis is usually shown around the ankle in outpatients, while bedridden patients usually have petechiae or ecchymosis behind their back. Petechiae can appear after a blood pressure check. Physical examination in APCD cases can reveal signs of underlying liver disease or gastrointestinal malabsorption. Physical examination in APCD cases can reveal signs of underlying liver disease or gastrointestinal malabsorption.10

In the laboratory, blood tests in patients with APCD are as follows: prolonged prothrombin time (PT), prolonged activated partial prothrombin time (aPTT), and bleeding time in the normal range. The results of the clotting factor test in patients with factor II deficiency are as follows: in hypoprothrombinemia, the functional and antigenic levels of factor II decrease; in dysprothrombinemia, the functional level decreases and antigenic level stays normal or slightly decreases; in patients with isolated factor II deficiency, other clotting factor tests are normal; factor II deficiency due to liver disease, vitamin K deficiency, or use of vitamin K antagonists, other clotting factor tests found a decrease in all dependent factors of vitamin K (i.e. factor II, factor VII, factor IX, factor IX, factor X, and protein C).10

TREATMENT

APCD cases rarely happen so there is no standard therapy used. Treatment aimed at controlling bleeding and removing inhibitors either with immunosuppressive therapy or treatment of the underlying disease.11 Treatment of APCD is intended to restore factor II to circulation in sufficient quantities to maintain hemostasis. An increase of more than 30% of normal is usually sufficient.8 Supportive therapy can be given with vitamin K, fresh frozen plasma (FFP), packed red blood cells (PRBC), platelets (thrombocyte), prothrombin complex concentrates (PCC), and recombinant factor VIIa.12 In addition, the treatment must also be based on APCD causes. Treatment options include: FFP infusion is sufficient to treat most bleeding cases, given intravenous bolus (IV) at a dose of 15-20 mL/kgbw, followed by a maintenance dose of 3-6 mL/kgbwIV in 12-24 hours; Plasma transfusion can be used to increase the number of factor II before surgery; PCC is used to increase the number of factor II, PCC contains factors II, VII, IX, and X plus protein C, but PCC must be used wisely because it involves thromboembolic complications; and, giving vitamin K is beneficial for patients with APCD.13

The aim of pharmacotherapy in patients with factor II deficiency is to reduce morbidity and prevent complications. Agents used include FFP, PCC, and vitamin K.6 Blood products are indicated for abnormal hemostatic parameters. Plasma is a blood fluid compartment that contains a dissolving clotting factor. Indications for using FFP include bleeding in patients with congenital coagulation defects and multiple coagulation factor deficiencies (severe liver disease).3

Patients who experience bleeding in warfarin therapy need a normalization ratio test and need a vitamin K concentrate and, or prothrombin complex. Patients who experience bleeding when using oral anticoagulants require a broader approach. Liver disease produces complex hemostatic changes, and management of bleeding depends on the location and severity of the bleeding. Disseminated intravascular coagulation complicates in many clinical conditions and requires immediate action when the patient experiences bleeding.1

The American Academy of Pediatrics (AAP) in 2003 recommended giving a single dose of vitamin K
0.5–1 mg in all newborns. The Indonesian Ministry of Health, the technical team from the Health Technology Assignment (HTA), and professional organizations have carried out studies on the administration of vitamin K1 to newborns since 2002 and recommend that all newborns should receive 1 mg of intramuscular vitamin K1 prophylaxis (recommendation A). Vitamin K injection plays an important role in two ways. First, vitamin K enters the infant’s circulation and immediately increases the amount of vitamin K in blood, so vitamin K levels in infants do not decrease very low in the first few days of life. Most of the vitamin K will be stored in the liver and used by the clotting system. Second, the remaining vitamin K is released slowly for 2-3 months, providing a constant source of vitamin K until the infant has other sources of diet.

Pregnant women who take anticonvulsant drugs should receive prophylactic vitamin K1 5 mg / day during the third trimester or 10 mg i.m, 24 hours before delivery. Then, the infant was given vitamin K1 1 mg i.m and repeated 24 hours later. Infants suspected of having APCD must receive vitamin K1 treatment 1-2 mg / day for 1-3 days immediately. Treatment response is expected to occur in 4-6 hours, marked by cessation of bleeding and improvement in physiological hemostasis. In term infants, if it does not improve within 24 hours, other causes must be considered, such as liver disease.

Corticosteroids are considered to work by slowing down the clearance of complex antithrombin and have been considered as first-line therapy. Other immunosuppressive therapies, primarily aimed for treating underlying autoimmune disorders, including intravenous immunoglobulin, cyclophosphamide, rituximab, and azathioprine.

Corticosteroids (methylprednisolone intravenously 40 mg every 6 hours, then oral prednisone 1 mg / kgbw daily) and intravenous immunoglobulin can slowly increase PT and aPTT. However, there is a little effect in bleeding. Treatment with active PCC is not carried out initially because of the potential risk for thrombosis associated with a simultaneous increase in factors VII, IX, and X in addition to the expected increase in factor II. Rituximab is preferred over cyclophosphamide to avoid the potential complications of hemorrhagic cystitis that will not be diagnosed easily. By one dose of rituximab, the factor II level increased to 264%, with the next plateau around 100%. When a patient presents with hemorrhagic diathesis without a history of coagulopathy, the presence of inhibitor factors must be considered immediately.

There are no dietary restrictions in individuals with factor II deficiency. Patients are advised to limit alcohol consumption to reduce the risk of alcohol-induced liver disease. Physical activity is regulated based on the severity of the APCD and the presence or absence of symptoms. Because of the risk of bleeding after a traumatic injury, activities with a high level of physical contact are not recommended. During pregnancy and preparation for having children, parents must be informed about the importance of vitamin K prophylaxis and each hospital must have a clear written protocol for administration of prophylactic vitamin K in newborns.

Fat-soluble vitamins have an important role in the function of clotting factors. Fat-soluble vitamin K is absorbed by the intestine and stored in the liver. Required for the function of clotting factors in the coagulation cascade. Used to replace essential vitamins that are not obtained in sufficient quantities in food (Bhat RV, Deshmukh CT. A study of Vitamin K status in children on prolonged antibiotic therapy. Indian Pediatr. 2003 Jan. 40(1):36-40). Vitamin K in breast milk has a major role in the pathogenesis of APCD disease. Intramuscular vitamin K1 prophylaxis should be routinely given to all newborns who will receive breast milk.

Almost all countries in the world have recommended the given of vitamin K1 prophylaxis in newborns. Using Konakion® 1 mg, a single IM dose since the 1970s has been widely used, especially in Australia. Initially these measures were only given to sick infants such as infants who were less than a month or perinatal asphyxia until finally as is now something routine to do. All newborns are recommended to receive prophylactic vitamin K1, healthy newborns.
should receive vitamin K either IM 1 mg, single dose at birth or 3 oral doses of 2 mg each given at birth at 3-5 days and ages 4-6 weeks.⁶

REFERENCES


