The Turkish Journal of Pediatrics 2018; 60: 429-432
DOI: 10.24953/turkjped.2018.04.012

Case Report

Venous thromboembolism in two adolescents with Down syndrome

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Received: 26th April 2017, Accepted: 4th July 2017

SUMMARY: Kurokami T, Takasawa R, Takeda S, Kurobe M, Takasawa K, Nishioka M, Shimohira M. Venous thromboembolism in two adolescents with Down syndrome. Turk J Pediatr 2018; 60: 429-432.

Although venous thromboembolic events are relatively rare in children, they are an increasingly recognized clinical entity in pediatric tertiary care hospitals. Although vascular disorders are prevalent with Down syndrome, it remains unclear whether Down syndrome patients are at higher risk for venous thromboembolic events. We report two adolescent cases with Down syndrome who unexpectedly developed venous thromboembolism in a general care unit. Our cases had a few risk factors; laparoscopic radical surgery for Hirschsprung's disease with central venous catheterisation in Case 1, and bacterial hepatic abscess in Case 2. Despite preventive heparinization with catheterisation and minor surgery in Case 1 and non-sepsis in Case 2, bed rest for only a few days triggered sudden onset of deep vein thrombosis in lower limbs with pulmonary thromboembolism in both cases. We speculate that the characteristics of Down syndrome, including physical and behavioural problems, might cause venous thromboembolic events. Thus, we should pay more attention to the relationship specifically between venous thromboembolism and Down syndrome, especially in adolescents, and increase prevention, early detection and treatment efforts.

Key words: venous thromboembolism, Down syndrome, immobility, adolescent.

Although venous thromboembolic events (VTEs) are relatively rare in children, they are an increasingly recognized clinical entity in pediatric tertiary care hospitals. The exact incidence of pediatric VTEs is unknown, with estimates ranging widely from 0.07–0.49 cases per 10000 children.[1] Although, vascular disorders, such as cerebral venous sinus thrombosis (CVST) and artery occlusion, including Moyamoya disease, are prevalent with Down syndrome (DS).[2-5] few studies have examined the relationship between DS and the incidence of VTEs. It remains unclear whether DS patients are at higher risk for VTEs. Here, we report two adolescent cases with DS who unexpectedly developed VTEs in a general care unit.

Case Report

Case 1

A 14-year-old boy with DS and chronic constipation due to Hirschsprung's disease was admitted to Kawaguchi Municipal Medical Center for a laparoscopic radical surgery for Hirschsprung's disease. On admission, his general condition was good, and preoperative examination revealed no cardiac, hepatic, renal, or respiratory function abnormalities, or coagulation. His height was 145.9 cm and weight was 37.95 kg (BMI, 17.8 kg/m^2). He had severe intellectual disability and conductive hearing loss, but no congenital cardiac anomalies or thyroid dysfunction.

Laparoscopic radical surgery for Hirschsprung's disease was performed under general anesthesia without any complications or blood transfusion.

Because of difficulty in maintaining postoperative rest, continuous intravenous muscle relaxant infusion through central venous catheterisation (CVC) with heparinization by 10 U/kg/h heparin sodium was required, and extubation was performed on postoperative day (POD) 4. After extubation, his activity recovered and serum C-reactive protein (CRP) level decreased, but plasma D-dimer and fibrin degradation product (FDP) levels rapidly increased from POD 4 to POD 5 (D-dimer, 19.3 to 49.2 μg/ml; FDP, 51.0 to 100.3 μg/ml) without prolongation of prothrombin time and activated partial thromboplastin time. Coagulation and thrombotic screens (lupus anticoagulant, protein S, protein C, factor V Leiden and antithrombin III) were also normal. Thus, we performed contrast computed tomography (CT), which revealed deep-vein thrombosis (DVT) in lower limbs with pulmonary thromboembolism (PTE) (Fig. 1A, 1B). The patient showed no symptoms of respiratory distress, circulatory failure, edema, or lower limb redness; thus, additional heparinization by continuous intravenous infusion of a total of 20 U/kg/h heparin sodium was started from POD 6. Heparinization ended on POD 14 because plasma D-dimer and FDP gradually decreased to 8.9 μg/ml and 20.1 μg/ml, respectively, without any symptoms, and follow-up CT revealed disappearance of vascular thrombus. Severe hemorrhage during the course of treatment and subsequent relapse did not develop. The patient was discharged on POD 42 after environmental arrangement and excretion care guidance for the patient's family.

Case 2

A 14-year-old boy with DS presented to our emergency outpatient department because of fever and repeated vomiting. The blood test showed elevated inflammatory response (WBC, 7.8×10^9/L; CRP, 18.92 mg/dl) and contrast CT revealed the presence of an abscess in the right hepatic lobe; thus, he was admitted to our hospital with a diagnosis of bacterial hepatic abscess and started with intravenous administration of cefoperazone. His height was 145.5 cm and weight was 42.2 kg (BMI, 19.9 kg/m^2). The boy had a history of coil embolization for ductus arteriosus at 6 years of age, and a mild state of aortic regurgitation was detected by cardiac ultrasound. Coagulation and thrombotic screens were all normal.

On the 2nd day of the admission, the patient percutaneously received drainage surgery on the hepatic abscess under general anesthesia. After awaking from anesthesia, he was obviously confused and upset because of the presence of the drainage device. From the 3rd to 6th day, his activity markedly decreased, and he stubbornly kept the same posture and did not move on the bed. After the 7th day, he gradually increased movement on the bed, and regained the motivation to take a walk in the ward on the 10th day. On the 11th day, the blood test revealed re-elevation of inflammatory response (WBC, 8.3×10^9/L, CRP, 10.71 mg/dl); thus, cefoperazone was changed to meropenem. On the 13th day, he complained of femoral pain with pretibial edema, and a laboratory test revealed an elevated D-dimer level of 6.8 μg/ml. Ultrasonography did not detect the pulse wave in the left femoral vein and revealed that the vessel diameter did not change after pressing. Contrast CT revealed a lack of contrasted effect in the same portion of the vascular lumen, which indicated a diagnosis of DVT in the left lower limb (Fig. 1C). Although he did not have the symptom of respiratory distress, the partial lack of pulmonary blood flow by scintigraphy and contrast CT confirmed the additional diagnosis of PTE (Fig. 1D, 1E). On the 18th day, he was treated with heparin sodium and warfarin. Thereafter, DVT in the femoral vein was gradually reduced in volume without any adverse effect, and the level of D-dimer decreased to the normal range. On the 30th day, because the lesion of the liver abscess became sufficiently small and the elevated inflammatory response improved (WBC, 4.2×10^9/L, CRP, 0.45 mg/dl); the drainage device was removed and meropenem was terminated. On the 36th day, he was discharged from our hospital without subsequent relapse.

We obtained the informed consents of the participation from both families. The authors declare no financial relationship or conflict of interest associated with this research.

Discussion

The growing incidence of VTE in the pediatric population is hallmarked by two distinct age distributions, the neonatal period and adolescence.[6] In contrast to neonates and children, a variety of risk factors (RFs) and

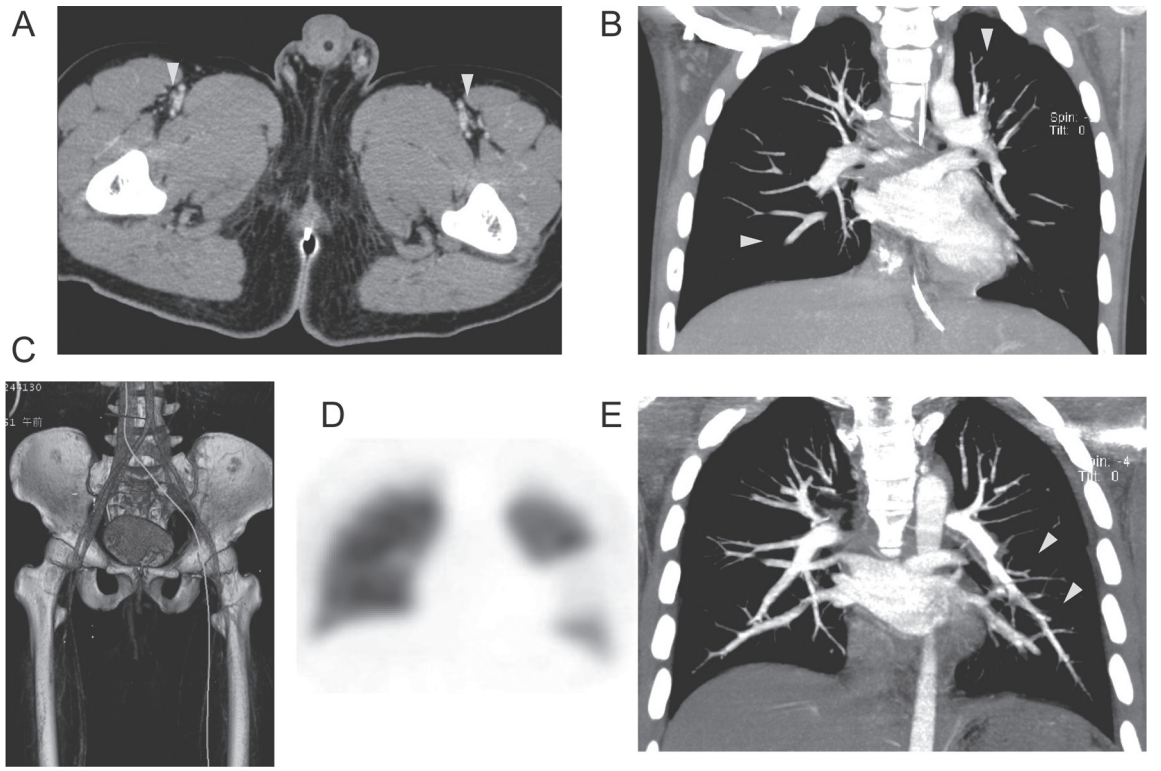

Fig. 1. Deep vein thrombosis and pulmonary thromboembolism images. A, B in case 1 and C–E in case 2. A. Postcontrast CT scan of lower limbs showing filling defects in the bilateral femoral veins (yellow arrowheads). B. Postcontrast chest CT scan showing filling defects in the bilateral pulmonary arteries; right A9 and left A1+2 (yellow arrowheads). C. 3D CT image of pelvofemoral veins showing filling defects from the left common iliac vein to femoral vein. D. Lung perfusion scintigraphy showing blood flow defects in the lingular segment of the left lung. E. Postcontrast chest CT scan showing filling defects in the left pulmonary arteries, left A8 and A9 (yellow arrowheads).

co-morbidities for VTE, including obesity, inflammatory bowel disease, hematologic malignancy and surgical procedures, have been described in the adolescent population.[7] The most common RF has long been attributed to CVC, but previous reports indicated that CVC may not be the only, or most important, RF in adolescents.[6] Therefore, several published guidelines on VTE prevention in hospitalised children described scoring systems for various RFs besides CV.[8]

Our cases of adolescents with DS developing VTEs had a few RFs: CVC and surgery in Case 1, and infection in Case 2. Despite preventive heparinization with CVC and minor surgery in Case 1 and non-sepsis in Case 2, VTEs were developed in both cases. Thus, we speculated that DS in adolescents might be at high risk for sudden onset of VTEs. Indeed, in a previous report, an adolescent case with DS who developed CVST had no RFs for thrombosis.[2,3] A previous retrospective analysis for children with cancer revealed that coexistence with DS increases VTE risk.[9]

Our cases indicated that immobility, which was caused by bed rest for only a few days, might be the main trigger of sudden VTW onset, as previously reported.[6,8,10] DS patients have substantial weakness in the strength of the knee extensor muscle[11], which is particularly pronounced during adolescence, because of the lack of physiological development of muscle strength observed in individuals with DS.[12] Consequently, adolescent DS patients might have a higher risk of venous stasis in lower limbs compared with adolescents without DS. Thus, we speculate that the sudden VTE onsets in our cases might occur easily, especially during adolescence, if immobility is a congenital RF of venous stasis.

Although the cause of generating immobility differed between cases 1 and 2, the pathogenesis was characteristic of the difficulties and complications prevalent with adolescent DS, respectively. With Case 1, we faced more

difficulty in physically controlling the patient's behaviour, because the adolescent was more physically mature. In addition, severe intellectual disability and conductive hearing loss, which are characteristic of DS[13], increased difficulty in linguistic interaction. Thus, excessive medical sedation during and after invasive procedures might be required, resulting in occurrence of excessive immobility. With Case 2, we experienced acute regression, which is a characteristic feature of adolescent DS.[14,15] Acute regression occurred as a result of reaction to acute stress and multiple environmental changes; the symptoms were sudden decrease in motivation and performance in daily life, and can lead to the loss of functional skills, including speech, toilet control, sleep apnoea and stubborn immobility. As a result of acute regression, difficulty in linguistic exchange increased, and we had no way to quickly recover mobility.

In conclusion, our cases highlighted that adolescents with DS are at high risk for sudden onset of VTEs. We speculate that the characteristics of DS, including physical and behavioural problems, might cause VTEs. Further accumulation of cases and prospective studies are needed to confirm association of DS and VTE, and explore potential mechanisms. We should pay more attention to the relationship specifically between VTE and DS, especially in adolescents, and increase VTE prevention, early detection and treatment efforts.

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