Deep Vein Thrombosis in Patients with Severe Motor and Intellectual Disabilities, Especially Diagnosis and Prevention of Recurrence for Chronic Thrombosis—Serial Changes of Sonography and D-Dimer

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Most patients with severe motor and intellectual disabilities (SMID) have restricted mobility capability and have been bedridden for long periods because of paralysis of the extremities caused by abnormal muscular tonicity due to cerebral palsy and developmental disabilities. Such patients are associated with a high risk of complications like deep vein thrombosis (DVT). Here, we report twelve patients (42.9%) with DVT among 28 patients with SMID during prolonged bed rest. However, we did not detect thrombosis in the soleal veins, finding it mostly in the femoral and common femoral veins. We applied anticoagulant therapy (warfarin), and carefully followed up the cases with DVT, regulating the warfarin dosage at prothrombin time-international normalized ratio (PT-INR) values around two to prevent recurrence of chronic thrombosis. Regarding laboratory data for the coagulation system, there were no cases above 5 µg/ml for the D-dimer and there were significant differences between the DVT and non-DVT groups in the D-dimer levels. The plasma levels of D-dimer in patients with DVT diminished to less than 1.0 µg/ml after warfarin treatment. Concerning sudden death (4.2%) in patients with SMID, we have to be very careful of the possibility of pulmonary thromboembolism due to DVT. Therefore, we should consider the particularity of the underdeveloped vascular system from underlying diseases for the evaluation of DVT. A detailed study of DVT as a vascular complication is very important for the smooth medical care of SMID, and serial assessment of compression Doppler ultrasonography of the lower extremities, as a noninvasive examination and measurement of D-dimer, is very helpful. (This article is a translation of Jpn J Phlebol 2014; 25: 34–42.)

Keywords: severe motor and intellectual disabilities (SMID), chronic deep vein thrombosis (DVT), D-dimer, ultrasonography

Introduction

To ensure the smooth provision of medical care for patients with severe motor and intellectual disabilities (SMID), it is very important that we deal with complications of the circulatory and vascular systems, in addition to complications of the respiratory system such as aspiration pneumonia. Most patients with SMID have motor paralysis of the extremities and restricted mobility due to abnormalities in muscle tone associated with cerebral palsy and developmental motor disabilities, among others.1,2 they are also associated with a high rate of complications of the vascular system, especially deep vein thrombosis (DVT).2–4 Following remarkable technological and pharmacological advances in neonatal care, the number of infants with severe brain impairment and respiratory problems has increased, particularly in extremely low-birth-weight infants. Among them, in those with profoundly severe motor and intellectual disabilities (p-SMID) who require particularly careful medical care and who have undergone tracheostomy and been placed under mechanical ventilation management, there are important tasks in home medical care.2,5,6 In
patients with SMID confined to bed and with decreased mobility of the lower extremities, there is prolonged bed rest and a higher risk of DVT complications.\(^2,3\) It has been reported that respiratory tract infections represent the most common cause of mortality in SMID, for which the rate of sudden death is over 4.2%\(^7\). In a previous study, we examined DVT in patients with SMID and found asymptomatic DVT at a high rate.\(^3\) DVT can have an asymptomatic clinical course, but many cases of DVT develop pulmonary thromboembolism (PTE), possibly causing sudden death.\(^8\)-\(^10\) In the present study, we closely investigated DVT of the lower extremities, especially the diagnosis and prevention of recurrence for chronic thrombosis and serial changes of ultrasonography and D-dimer in patients with SMID.

### Materials and Methods

#### Patients

Twenty-eight patients with SMID, who were classified as class 1 of Ohshima’s classification criteria for SMID (Fig. 1)\(^1\)(1) having physical and intellectual disabilities, including the inability to maintain a sitting position and being bedridden, were eligible for this study; they included those under intensive medical treatment with long-term hospitalization for SMID in the wards of the National Hospital Organization Yanai Medical Center (Table 1).

All of these patients had severely decreased mobility of the lower extremities and many required tube feeding, tracheostomy, mechanical ventilation, and nutritional management; there were 23 cases of tube feeding (five cases of nasogastric tube, 18 cases of gastrostomy), 11 cases of tracheostomy (three cases of mechanically ventilated patients and three cases had undergone laryngotraqueal separations), one case of noninvasive positive pressure ventilation, and 24 cases (85.7%) of epilepsy. All patients were observed for more than one year.

#### Methods

We evaluated DVT in deep veins of the lower extremities serially ongoing by venous sonography using a GE Healthcare LOGIQ-S6 or LOGIQ-e (GE Healthcare Japan) and an 8–12 MHz variable linear probe in the 28 patients.

We have followed up for patients detected with DVT at intervals of 3 to 6 months, and for patients not detected with DVT at intervals of about 6 months as far as possible. We endeavored to examine by ultrasonography in the supine position at the iliac and femoral regions, and in the supine position with drooping foot at the bedside in the popliteal and lower leg regions (especially intramural veins) because most patients with SMID could not maintain a sitting position, though the standard procedure is performed in the sitting position with fully congested blood flow of the lower veins.

For the diagnosis of DVT by venous ultrasonography, we confirmed a collapsed vein with the creation of vessels by B-mode ultrasound transverse imaging and compression of the probe, and on the basis of blocking of the blood flow by color Doppler ultrasonography with or without respiratory variation on a pulse Doppler method arbitrarily.
In addition, we specifically examined the blood coagulation test at intervals of one month, 3 months and 6 months, including D-dimer (refined measurement of latex agglutination method, criterion value under 1.0 µg/ml), which has high diagnostic specificity for DVT as a hematological assessment. Furthermore, in terms of the ethical aspects, we carried out our research, with anonymous clinical data under close supervision, after approval by the medical ethics committee of our hospital.

**Results**

The patients included 15 males and 13 females with a mean age of 45.5 years (from 8 to 74 years old). They had no symptoms in all cases, but 12 of the 28 cases (42.9%) showed DVT in the lower extremities asymptomatically (mean age of 46.1 years, six males and six females) (Table 2, Fig. 2). In the veins of the lower extremities in DVT formation, there were three cases in the right common femoral vein, two cases in the left common femoral vein, one case in the left superficial femoral vein + right posterior communicating branch, one case in the left posterior tibial vein + right posterior communicating branch, one case in the left common femoral vein + deep femoral vein + right posterior tibial vein, one case in the right common femoral vein + right posterior tibial vein, one case in the left common femoral vein + superficial femoral vein, and one case in the right great saphenous vein. Many cases were shown in superficial veins and the common femoral veins proximally to the soleus veins (Table 2). In the posture and limb position, there were no differences between the 12 cases of DVT and the 16 cases of non-DVT in terms of mobility, and all cases in the present study had deformities and contracture of the hip and knee joints, with 20 of 28 cases
Table 1

<table>
<thead>
<tr>
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<th>DVT group (n = 12)</th>
<th>Non-DVT group (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (sec)</td>
<td>11.59 ± 0.96</td>
<td>11.50 ± 1.14</td>
</tr>
<tr>
<td>PT (%)</td>
<td>94.98 ± 19.95</td>
<td>98.83 ± 22.80</td>
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<tr>
<td>PT-INR</td>
<td>1.050 ± 0.143</td>
<td>1.034 ± 0.144</td>
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<tr>
<td>APTT (sec)</td>
<td>31.35 ± 2.99</td>
<td>30.98 ± 5.25</td>
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<tr>
<td>Fib (mg/dL)</td>
<td>259.78 ± 48.16</td>
<td>287.38 ± 72.19</td>
</tr>
<tr>
<td>D-dimer (µg/mL) (&lt;1.0)</td>
<td>1.042 ± 0.463? (pre)</td>
<td>0.463 ± 0.436</td>
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<tr>
<td></td>
<td>0.267 ± 0.144 (post)</td>
<td>0.381 ± 0.256</td>
</tr>
<tr>
<td>FDP (µg/mL) (&lt;5.0)</td>
<td>2.92 ± 1.83</td>
<td>2.56 ± 1.03</td>
</tr>
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<td>AT-III (%) (75–125)</td>
<td>99.83 ± 14.72</td>
<td>104.75 ± 13.11</td>
</tr>
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*p < 0.05, pre: before anticoagulant therapy for DVT; post: after anti-coagulant therapy for DVT. DVT: deep vein thrombosis; PT (sec): prothrombin time; PT (%): prothrombin consumption test; PT-INR: prothrombin time-international normalized ratio; APTT: activated partial thromboplastin time; Fib: fibrinogen; FDP: fibrin/fibrinogen degradation products; AT-III: antithrombin III

having moderate to severe deformities of the spine (scoliosis) in the thoracolumbar region, and 10 of 28 cases having dislocation of the hip (three cases in bilateral sides, five cases in the right side including one case of right bone replacement, two cases in the left side) (Table 1). However, there were no differences between the DVT group and the non-DVT group in terms of orthopedic findings, and we received the impression that all cases had general narrowing of the vessels of the lower extremities, with or without effects of immature blood vessels or maldevelopment. Then, on examination of the intramuscular veins in the lower legs, we tried to examine at the bedside drooping legs and congested veins as far as possible, but as the examination is basically recommended to observe the patient in the sitting position, we cannot exclude the possibility that it was related to examination position as we could not find any DVT of the soleal veins.

Additionally, there were no differences in the thickness of the lower extremities in any cases. In the coagulation test, values of D-dimer (refined measurement of latex agglutination method, criterion value under 1.0 µg/ml) as a useful marker for the diagnosis of DVT in hematological assessment were above 1.0 µg/ml in 5 of 28 cases, above 0.5 µg/ml as a recurrence index in 17 of 28 cases, but were always under 5 µg/ml. There were significant differences between the DVT and non-DVT groups in the D-dimer levels before anticoagulant therapy (Unpaired Student t-test, p < 0.05) (Table 3). The plasma D-dimer levels in patients with DVT for serial assessment decreased to below 1.0 µg/ml after warfarin treatment at the time of 6 months. There were no marked abnormalities in the values of protein C, protein S, anti-thrombin III, and anticardiolipin antibody. In 12 cases of DVT in the lower extremities by venous ultrasonography, we initially gave warfarin for over 6 months and carefully followed up the cases, regulating the warfarin dosage at PT-INR values around two and with clinical examination and venous ultrasonography in the lower extremities. Also, we did not use elastic compression stockings for effective medical care of chronic thrombosis because the thrombotic lesions were mainly in superficial veins and common femoral veins.

Discussion

There are certain main risk factors for pulmonary thromboembolism (PTE), specifically, protein C deficiency, protein S deficiency, antithrombin deficiency as congenital risk factors, and surgery, obesity, bed rest, malignancy (Trousseau syndrome), trauma, fracture, insertion of a central intravenous catheter, congestive heart failure, chronic pulmonary diseases, cerebrovascular disorders, antiphospholipid antibody syndrome, and drugs (estrogen, oral contraceptive, steroid, etc.), among others, as acquired risk factors. Over 90% of cases of embolus of acute PTE involve thrombus of a vein in the lower extremities or pelvis, and in DVT of veins in the pelvis and lower extremities, patterns of the disease are divided into a central type (iliac and femoral type) from the popliteal vein centrally and a peripheral type from the popliteal vein distally (crural type). The crural type accounts for the largest proportion of DVT, and the main initial region of DVT in the lower extremities has been reported to be the soleal vein. Prolonged bed rest, advanced age, malignancy, obesity, and hypercoagulable status, among others, are persistent risk factors. Patients with SMID are seriously restricted in mobility due to motor impairment due to motor disabilities and, among them, patients with grade 1 of Ohshima’s classification, who are incapable of maintaining a sitting position, require critical care such as respiratory and nutritional management, especially when undergoing long-term tube feeding from disuse atrophy in association with a bedridden state and difficulty in swallowing. As a result, they may have an extremely high risk for DVT from prolonged immobility. In the Japanese Guidelines for the Prevention of Venous Thromboembolism (revised edition, 2009), it has been reported that the clinical conditions of prolonged bed rest, paralysis of the lower extremities, and spinal injury, among
other things, are risk factors for DVT. In the present study, we found a significant rate of DVT of 42.9% (12/28 cases) in patients in a bedridden state, with severely decreased mobility of the lower extremities and tube-feeding, and receiving respiratory care by tracheostomy and/or mechanical ventilation. However, in the region of thrombus formation with DVT, mostly the superficial femoral vein and the common femoral vein centrally to popliteal veins were involved, and we did not detect DVT in the soleal vein, which was previously reported as the initial site of DVT.\(^{19,20}\)

In terms of clinical manifestations, especially the peripheral type of DVT, pain is common, although conversely, there are often no symptoms. In addition, most patients with SMID have communication difficulties and we thus need to observe the potential clinical symptoms of DVT carefully. Therefore, it is very difficult to understand the pathogenesis of DVT accurately.

To diagnose DVT clinically, phlebography of the lower extremities is the most reliable standard test for confirming the diagnosis of DVT, even now, but it is only a candidate approach in cases not diagnosed by other imaging methods because of an intensely invasive procedure.\(^{15}\)

This is because it cannot be performed easily on bedridden patients with SMID owing to the troublesome transfer to a clinical laboratory because of intensive medical care such as tracheostomy and mechanical ventilation. On the other hand, venous sonography of the lower extremities is generally used via a compression procedure as a non-invasive test, and we could obtain precise imaging findings more easily at the bedside using portable ultrasound instruments.\(^{13,20,21}\) It is a very useful diagnostic method for the evaluation of DVT in patients with SMID with restricted motility.

In our present investigation, we could not detect thrombus in the soleal vein as the initial site of DVT in the deep veins of the lower extremities, but did so in the left common femoral vein, left superficial femoral vein, right common femoral vein, right superficial femoral vein, and the bilateral posterior tibial vein communicating branch centrally to popliteal veins. In cases with thrombi and occlusion in the fibular and posterior tibial veins, there could have been pre-existing thrombi in the soleal veins. It is possible that we failed to visualize thrombi in the soleal vein by venous sonography in the lower extremities and it is difficult to clarify the existence of previous thrombi in the soleal vein. However, it is considered that thrombus formation is causally related to disturbance of mobility due to a prolonged bedridden state related to cerebral palsy from young childhood, especially due to paralysis of the lower extremities, which leads to contracture deformities of the lower extremities and concomitant narrowing of the vessels by vascular underdevelopment and immaturity.\(^{22,23}\)

Consequently, it has been suggested that thrombus forms in the conduct veins centrally in patients with SMID. We only detected it mainly in the common femoral and superficial veins, there were no associations with significantly elevated levels of D-dimer caused by reduced vessel volume due to vascular underdevelopment and immaturity.

On the other hand, the D-dimer value is in widespread use for early diagnosis of DVT and PTE and a valuable marker for screening of DVT. To return toward a normal range of D-dimer has become helpful in the assessment for duration or completion of anticoagulant therapy.

It has been reported that D-dimer values decrease as a result of heparin therapy for DVT, but there are few reports to assess D-dimer values serially in patients with DVT.\(^{14}\)

In the present study, the plasma D-dimer levels in all patients with DVT decreased to below 1.0 µg/ml after warfarin treatment.

As therapeutic management, heparin and warfarin for anticoagulant drugs have been commonly used\(^{14,15,24-26}\) and the initiation of heparin and warfarin combined therapy has been required because of the high recurrence rates of warfarin alone.\(^{15}\)

In this research with SMID, there are definite risk factors such as prolonged bedridden, among others for chronic DVT with SMID and we provided warfarin therapy mainly giving attention to the risk of bleeding from the aspect of prevention and recurrence of DVT.

In the Japanese Guidelines for the Prevention of Venous Thromboembolism (revised edition, 2009),\(^{15}\) prothrombin time is described as acting as a general indicator of warfarin dosage for DVT, and the dosage is regulated with reference to the international normalized ratio (INR). That is, warfarin at a daily recommended dose of 5 mg has been administered for the first two days of therapy, and the PT-INR levels are controlled in the range of 1.5 to 2.5 (desired value 2.0). In cases with irreversible risk factors, warfarin is administered for 3 months, and in cases having relapse and persistent risk factors, warfarin is considered to be given chronically. We investigated for the purpose of finding a clearly useful guideline in properly-based therapy in DVT patients with SMID as a result of no definite criteria in the completion of warfarin therapy.

We studied chronic vein thrombosis with SMID in the lower extremities under SMID with restricted motility and disability as risk factors. We gave warfarin carefully in consideration of the advantages and disadvantages for over 6 months and carefully followed up the cases, regulating the warfarin dosage at PT-INR values around 1.5 and with clinical examination of D-dimer and venous ultrasonography serially. As a result, the plasma D-dimer levels in all patients with DVT decreased and some of them with DVT showed diminished thrombi. Also, as the patients with SMID have poor development of the muscles of the lower leg, especially
the soleus muscle, we did not use elastic stockings for chronic thrombosis because of the scarce evidence of any indication for stockings in patients with SMID.

To use the elastic compression stockings for chronic thrombosis improves venous reflux to the microcirculation due to compression of the lower leg muscles, enables over a long time period and are more effective combined with physical therapy of extension upward of the lower legs. In the future, we need to apply the stockings over the entire lower leg to DVT with SMID. In patients with SMID seriously restricted in mobility due to motor impairment due to cerebral palsy, among others, and in a bedridden state, we need to give anticoagulant therapy carefully for over 6 months with serial examination of D-dimer values and venous ultrasonography over this time period.

DVT mostly remains asymptomatic and has been detected only at the onset of PTE.

A sudden death rate of 4.2% has been reported among the causes of death in patients with SMID, after pneumonia, respiratory failure, heart failure, and asphyxia. Right ventricular hypertrophy was found in only five cases of seven autopsies for the clinical consideration of sudden death in patients with SMID, but it cannot be ruled out that DVT may have developed into PTE because these cases were not specifically examined for the involvement of the pulmonary arteries.

The non-surgical patients with markedly high D-dimer levels indicate a high possibility of acute phase DVT and the patients with a modest increase or not-increased D-dimer levels has suggested chronic phase DVT. For the assessment of DVT with SMID, especially chronic phase DVT, it is necessary for highly-sensitive measurement of D-dimer as in ELISA (enzyme-linked immunosorbent assay) methods. Furthermore, other clinical conditions, such as pneumonia, show also the elevation of D-dimer, and increased D-dimer levels do not exactly suggest the presence of thrombosis and recurrent DVT. There are still basic problems for the evaluation of elevated D-dimer levels as to whether they are indicating thrombosis and recurrence of DVT or not. Although, we obtained blood samples at clinical, had a febrile stable condition, and performed serially venous ultrasonography of the lower extremities and detected the thrombosis and so the elevated D-dimer levels could indicate thrombosis and recurrent DVT.

In the future, it will be very important to assess and investigate closely DVT as a cardiovascular complication in order to ensure quality of life and to provide detailed medical support to patients with SMID. To diagnose DVT, in particular recurrence of DVT, it is very helpful to perform ultrasonography of the lower extremities as a non-invasive examination and to measure serum D-dimer values.

Disclosure Statement

Hiromitsu Ohmori and the coauthors have no conflicts of interest to disclose.

References