Lupus anticoagulant and protein S deficiency in a child who developed disseminated intravascular coagulation in association with varicella

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SUMMARY: Kurugöl Z, Vardar F, Özkınay F, Kavaklı K, Çetinkaya B, Özkınay C. Lupus anticoagulant and protein S deficiency in a child who developed disseminated intravascular coagulation in association with varicella. Turk J Pediatr 2001; 43: 139-142.

Varicella is not always a benign disease it may cause serious complications. We report a two-year-old boy with disseminated intravascular coagulation in association with varicella. The patient had the lupus anticoagulant, the antiphospholipid antibody, acquired free protein S deficiency, and increased concentrations of the prothrombin F 1+2 fragment. Intravenous immunoglobulin was administered due to its potential antibody-blocking activity, and the patient responded well. We recommend that children with varicella and disseminated intravascular coagulation should be examined for the lupus anticoagulant, the free protein S antigen, the prothrombin fragment F 1+2 and the other coagulation parameters. Intravenous immunoglobulin administration could be useful in such conditions because of its antibody-blocking activity.

Key words: protein S, lupus anticoagulant, varicella, disseminated intravascular coagulation.

Varicella is generally benign in healthy children and the complications of disease are not common[1]. However, recent epidemiological studies suggest that varicella complications may be more frequent than previously reported[2-5]. Life-threatening thrombotic complications such as purpura fulminans, disseminated intravascular coagulation, and thrombosis have been rarely reported in children with varicella[6,7]. Investigators have described children with thromboembolism and acquired protein S deficiency in association with varicella[8-11].

We report the occurrence of disseminated intravascular coagulation in a case with varicella. The patient also had a lupus anticoagulant (LA) and acquired free protein S deficiency.

Case Report

A two-year old boy was admitted to our hospital with the complaints of fever, cough and dyspnea for four days. He had been diagnosed with varicella 10 days previously. He was a healthy child before varicella infection. There was no family history of thrombosis.

On admission, physical examination revealed tachypnea, intercostal, subcostal and suprasternal retractions, and rales at both lung fields. The patient was febrile (temperature 38.2 °C). The hemoglobin level, and the white cell and platelet count were normal. The erythrocyte sedimentation rate and the concentrations of C-reactive protein were slightly elevated. Activated partial thromboplastin time (APTT) and prothrombin time (PT) were normal. Tests of liver and kidney function were normal. The serum immunoglobulin levels and lymphocyte subgroups were within the normal range. No pathogenic microorganism was detected in cultures taken from the throat, urine, blood or stool. Anti-varicella IgG and IgM antibodies were positive. Chest x-ray showed bilateral nodular infiltrates throughout both lung fields.

Therapy was started with intravenously administered ceftriaxone 100 mg/kg/day and acyclovir 1500 mg/m^2/day, but the patient did not respond. Three days after his admission he developed hematemesis, generalized tonic-clonic convulsions and subconjunctival hemorrhage in the temporal chamber of the right eye.

Funduscopic examination and cranial computed tomography were normal. Cerebrospinal fluid examination revealed a slightly elevated protein concentration with no pleocytosis. There was no growth in the cerebrospinal fluid culture. Thrombin time (TT) and APTT were prolonged (Table I). Platelet count and fibrinogen were decreased. D-dimer level was extremely elevated (7.24 μg/ml). Protein C and antithrombin activity were determined with Sta-Compact Analyzer Coagulometry using Diagnostica Stago (Asniéres, France) kits. The thrombin antithrombin (TAT) complex and the prothrombin fragment F 1+2 (PF 1+2) were measured with an ELISA (Enzygnost, Dade-Behring/Germany). Free protein S antigen, tissue plasminogen activator (tPA), plasminogen activator inhibitor 1 (PAI-1) and antiphospholipid antibody (APA) were assessed by ELISA (Asserachrom, D.Stago/France). Activated protein C-resistance (APC-resistance) was measured using Dignostica Stago kits. Lupus anticoagulant was determined by Staclot-PNP (D.Stago/France). The results of the tests were compared with the results of healthy children reported by Andrew et al[12]. Protein C activity was normal (Table I). Free protein S concentration was markedly reduced (0.21 U/ml). The concentrations of PF 1+2, TAT complex, tPA and PAI-1 were elevated. Lupus anticoagulant was positive, and APA was elevated.

A diagnosis of disseminated intravascular coagulation was considered. Infusion of fresh frozen plasma and intravenous immunoglobulin (400 mg/kg/day, for 5 days) were given. Clinical symptoms improved rapidly, and disseminated intravascular coagulation was controlled with the normalization of PT, APTT, fibrinogen and platelet count. However, free protein S remained below the normal range (0.31 U/ml) and LA was positive. The concentration of PF 1+2 was found to be slightly elevated (1.36 nmol/L). The concentrations of tPA, PAI-1, TAT were increased (Table I).

One month after admission, all coagulation parameters including free protein S antigen and PF 1+2 were normal. Lupus anticoagulant also disappeared (Table I).

Family investigation was normal in terms of hemostasis. Protein S was normal in both parents and sister.

Discussion

Varicella may be associated with severe purpura fulminans and disseminated intravascular coagulation [7,8]. In the patient presented here, the disseminated intravascular coagulation was diagnosed by the determination of prolonged APTT and TT, elevated D-dimer levels and a decreased platelet count.

Table I. Laboratory Findings of the Patient on the 3rd, 7th and 30th Days of Admission

	On the 3rd day	On the 7th day	On the 30th day
PT (s)	14	13	12
APTT (s)	42	30	28
Platelet count (/mm³)	101000	207000	260000
Fibrinogen (g/dl)	1.60	2.60	3.66
D-dimer (μg/ml)	7.24	2.2	0.42
Thrombin time (s)	23	22	19.1
Protein C (U/ml)	0.49	0.49	0.92
Free protein S (U/ml)	0.21	0.31	0.72
PF 1+2 (nmol/L)	1.66	1.36	0.67
TAT (μg/L)	18.32	6.5	3.61
tPA (ng/ml)	23.6	20.3	11.94
PAI-1 (ng/ml)	75	75	40
APC-resistance	150	155	145
Lupus anticoagulant	+	+	-
APA (UPL/ml)	41.46	27.8	14.2

PT ..... : prothrombin time.
APTT ..... : activated partial thromboplastin time.
PF 1+2 ..... : prothrombin fragment F 1+2.
TAT ..... : thrombin antithrombin complex.
tPA ..... : tissue plasminogen activator.
PAI-1 ..... : plasminogen activator inhibitor.
APC-resistance ..... : activated protein C-resistance.
APA ..... : antiphospholid antibody.
The reference ranges [12] for PT: 12-16 s.
APTT ..... : 25-33 s, thrombin time: 15-22 s.
fibrinogen ..... : 1.7-4 g/dl.
D-dimer ..... : <0.5 μcg/ml.
protein C ..... : 0.40-0.92 U/ml.
free protein S antigen : 0.71-0.97 U/ml.
PF 1+2 ..... : 0.4-1.1 nmol/L.
TAT ..... : 1.0-4.1 μg/L.
tPA ..... : 1-12 ng/ml.
PAI-1 ..... : 4-43 ng/ml.
APC-resistance ..... : > 75%.
APA ..... : < 15 UPL/ml.

Protein S is a plasma protein involved in the regulation of the protein C anticoagulant pathway. Free protein S is the active plasma form of protein S with anticoagulant activity. Several cases of varicella associated with severe thromboembolism and isolated acquired free protein S deficiency have been reported[8,9]. Recently, the presence of the LA has been described in children with varicella who acquired protein S deficiencies[10]. We also found the LA in association with acquired free protein S deficiency. In addition, our patient had increased concentrations of PF 1+2, tPA and PAI-1. The prothrombin fragment F 1+2 is generated when prothrombin is converted to thrombin, and is a current marker of excessive thrombin generation. In our patient, increased concentration of the PF 1+2, in our opinion, suggested the presence of excessive thrombin and hypercoagulability. The prothrombin fragment F 1+2 returned to normal levels when LA and protein S deficiency had resolved. This observation suggests that reduction in free protein S and LA may exacerbate the disseminated intravascular coagulative response. However, it is not clear whether the acquired protein S deficiency and the LA are the causes or the consequences of disseminated intravascular coagulation.

In our patient, the elevated D-dimer level and prolonged TT were considered due to the thrombosis in the microvascular plexus, and increased tPA, PAI-1 and D-dimer levels probably reflected that the fibrinolytic system was activated secondary to extensive microvascular thrombosis.

Currently, protein S concentrates are not available. Therefore, replacement with fresh frozen plasma might be the best alternative strategy in patients with protein S deficiency in association with varicella. However, because fresh frozen plasma contains only a small amount of protein S and has potential risks, the use of fresh frozen plasma has not been recommended by some authors [13,14]. Our patient was given fresh frozen plasma as a supportive therapy for disseminated intravascular coagulation. We could not use heparin due to hematemesis.

Recently, autoantibodies against protein S were shown in patients with protein S deficiency in association with varicella, and it has been reported that protein S antibodies may result in acquired free protein S deficiency [8,10]. The nature of the protein S antibodies is unclear; it has been postulated that the protein S antibodies may be the LA[10]. Because of the presence of the LA in our patient, we decided to administer intravenous immunoglobulin due to its potential antibody-blocking activity. Our patient responded well to its administration.

In conclusion, varicella is not always a benign disease of childhood. It may cause serious complications such as disseminated intravascular coagulation and thrombosis. Clinicians should be aware of thromboembolic complications. We recommend that children who develop disseminated intravascular coagulation in association with varicella should be examined for the LA, the free protein S antigen, the PF 1+2 and other coagulation parameters. Intravenous immunoglobulin administration could be useful in such conditions because of its antibody blocking activity.

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