NONTRAUMATIC BILATERAL SUBDURAL HEMATOMA CAUSED BY ANTIAGGREGATION THERAPY: CASE REPORT AND REVIEW OF THE LITERATURE

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SUMMARY – A 64-year-old female receiving clopidogrel and aspirin antiaggregation therapy after percutaneous coronary intervention for non-STEMI myocardial infarction developed nontraumatic bilateral subdural hematoma with dizziness, vertigo and headache. Craniotomy had to be postponed because of reduced ADP platelet aggregability. Four days after clopidogrel withdrawal and transfusion of 12 platelet concentrate units, ADP aggregation transiently normalized and bilateral trepanation with hematoma evacuation was performed. The procedure was followed by excellent neurologic and clinical recovery; however, decreased platelet aggregability was recorded by postoperative day 12 despite strict clopidogrel and other platelet inhibitor withdrawal. Suspicion of Glanzmann thrombastenia was excluded by flow cytometry. Two weeks after neurosurgery, the right femoral vein thrombosis was detected by color doppler ultrasonography and therapy with fractionated heparin was initiated, followed by warfarin. The risk and incidence of hemorrhagic complications of antiaggregation and anticoagulation therapy are discussed. Caution is warranted on prescribing this potentially harmful therapy to older patients, generally burdened with other chronic comorbidities.

Key words: Key words: *Hematoma, subdural – diagnosis; Hematoma, subdural – etiology; Hematoma, subdural – therapy; Anticoagulants – therapeutic use; Disease progression; Aged; Case report*

Introduction

Nontraumatic chronic subdural hematoma is a frequent clinical entity in daily neurosurgical routine. It usually occurs in elderly people with a peak incidence in the eighth decade of life[1]. Studies have identified age, sex, falls, and anticoagulant or antithrombotic therapy as the major risk factors for the development of chronic subdural hematoma. The higher incidence of chronic subdural hematoma in those older than 65 is associated with fragility of the bridging cerebral veins due to brain atrophy, a higher tendency to falls, and more common use of anticoagulant (warfarin) and antithrombotic (aspirin and clopidogrel) therapy. In addition, brain movements facilitate arachnoid membrane tearing even with trivial trauma. The male predominance is also associated with greater exposure to injuries. Previous trauma in combination with anticoagulant or antithrombotic therapy may also increase the risk of chronic subdural hematoma. Review articles report on a varying proportion of patients with chronic subdural hematoma, describing it as a condition accompanying arterial aneurysm rupture, lumbar puncture, anticoagulant therapy, acquired coagulopathy and thrombocytopenia[1-5].

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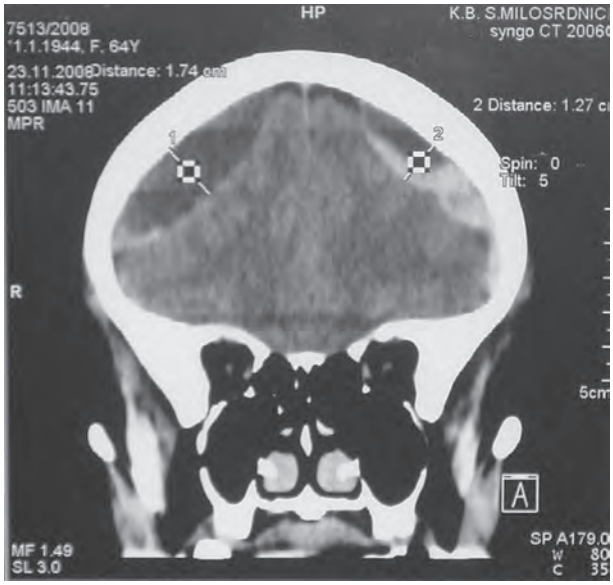

Fig. 1. Computed tomography image of bilateral subdural hematoma.

Case Report

A 64-year-old female patient was admitted for weakness, mental confusion, orthostatic instability, and urinary incontinence. The patient denied previous injuries and bleeding episodes. Her mother died from cerebrovascular thrombosis and her father from myocardial infarction. Her personal medical history included long-term hypertension, type 2 diabetes, and hyperlipoproteinemia. Two years before, she had undergone percutaneous angioplasty for anterolateral (non-STEMI) myocardial infarction, upon which ischemic pain resolved and she was discharged from the hospital on dual antiaggregation therapy with aspirin and clopidogrel. In two months, however, the patient experienced recurrent episodes of ischemic chest pain; repeat coronarography revealed 60%-70% stenosis of a distal segment of the left coronary artery, 70% stenosis of the left anterior descending artery (LAD), and 90% stenosis of the proximal D1 segment, which was managed by endoprosthesis placement. In addition, there was subocclusion of a proximal segment of the hypoplastic circumflexed coronary artery, which had formed collaterals to the right coronary artery. Dual antiaggregation therapy (aspirin and clopidogrel) was continued and unfortunately complicated by bleeding duodenal ulcer four months later. After short therapy discontinuation, clopidogrel therapy was reintroduced because coronary disease was considered to pose greater risk than gastroduodenal bleeding.

Ten months later, the patient presented with bilateral subdural hematoma (Fig. 1). Neurosurgical treatment was indicated but evacuation of the hematoma had to be postponed due to reduced (13%) ADP pathway platelet aggregation. Other biochemical parameters were normal (Table 1). Four days of clopidogrel withdrawal and platelet transfusion, the ADP-induced platelet aggregation normalized (78%) (Table

Table 1. Blood parameters at admission

Parameter	Measured value	Unit	Reference value
Platelet aggregation response to ADP	13	%	64-86
Platelet aggregation response to epinephrine	67	%	59-93
Platelet aggregation response to collagen			59-93
Red blood cells (female)	67	%	3.8 - 5.1
Hemoglobin (female)			11-16
White blood count (female)	4.5	$x10^6/\mu L$	3.8-11
Platelets	122	g/dL	150-350
Prothrombin time	6.6	$x10^3/mm^3$	70-130
Fibrinogen	227	$x10^3/mm^3$	
Activated partial thromboplastin time	97	%	
Thrombin time	5.9	g/L	
Fibrinolysis	26	sec	
	19	sec	
	210	min	

ADP = adenosine diphosphate

Table 2. Blood tests on day 4 of treatment

Parameter	Measured value	Unit	Reference value
Platelet aggregation response to ADP	78	%	64-86
Platelet aggregation response to epinephrine	71	%	59-93
Platelet aggregation response to collagen	76	%	59-93

ADP = adenosine diphosphate

2). Bilateral trepanation and hematoma evacuation were performed and resulted in excellent neurologic recovery. The patient was discharged from the hospital; however, on postoperative day 14 she was readmitted for the left iliofemoral vein thrombosis diagnosed by doppler ultrasound. The previous hypocoagulation condition caused by antiaggregation therapy had now turned to a thrombophilic (hypercoagulation) condition due to recent brain surgery (thromboplastin release), bed rest (retarded venous flow), and urinary infection (inflammatory cytokines, fibrinogen). The patient was administered heparin, followed by warfarin in a slightly reduced dosage because of bleeding episodes in her recent medical history, with good clinical response. Aggregation tests were repeated to show reduced platelet aggregability in spite of taking no antiaggregation therapy (Table 3). This finding raised suspicion of underlying yet undiagnosed Glanzmann thrombasthenia; however, flow cytometry was negative for CD42 (GPIIb) and CD61(GPIIIb) (Table 1).

Discussion

The majority of patients with chronic subdural hematoma are men older than 65, with a history of head trauma, or taking anticoagulant and/or antiaggregation therapy. Older age is associated with a higher likelihood of brain atrophy and bridging vein fragility, the risk of falls and frequent use of anticoagulant and antiaggregation therapy. The incidence of chronic subdural hematoma has been estimated to 5.3 *per* 100,000 surgically treated individuals. Previous head trauma is reported in 60%-80% of cases; however, mild traumatic events may proceed unrecognized, leading to an increased proportion of allegedly 'spontaneous' cases of chronic subdural hematoma[6].

Diagnostic procedure for chronic subdural hematoma has been well established and includes neuroimaging techniques of multi-slice computed tomography (MSCT) and magnetic resonance imaging (MRI)[2,7]. Density of blood coagulum varies with the age of hematoma; therefore, after three weeks, a chronic hema-

Table 3. Blood tests on day 15 of trephination

Parameter	Measured value	Unit	Reference value
Platelet aggregation response to ADP	56	%	64-86
Platelet aggregation response to epinephrine	55	%	59-93
Platelet aggregation response to collagen	49	%	59-93
Prothrombin time	95	%	70-130
Fibrinogen	5.0	g/L	
Activated partial thromboplastin time	26	sec	
PFA 100 collagen/epinephrine	112	sec	
von Willebrand's factor	>149.70		82-150

ADP= adenosine diphosphate; PFA = Dade Behring PFA-100 platelet function analyzer; it also measures *ex vivo* platelet binding to collagen/epinephrine (CEPI) or collagen/adenosine diphosphate (CADP)

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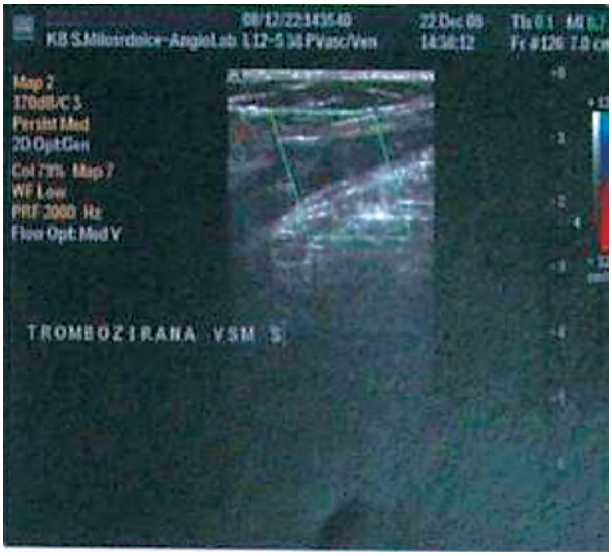

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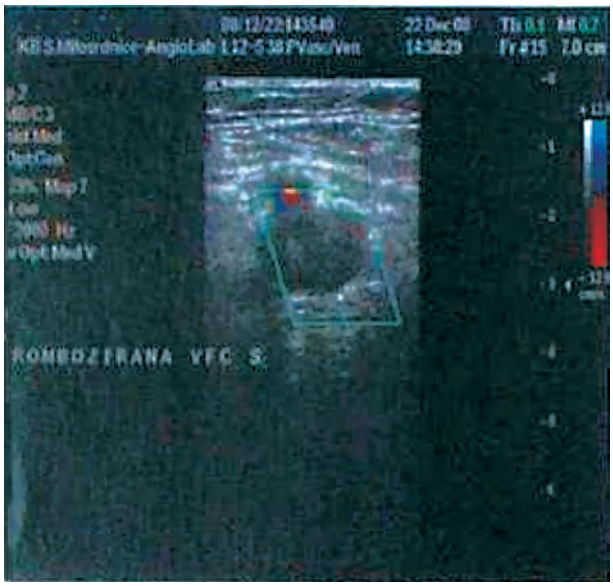

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Fig. 2. Ultrasonographic image of venous thrombosis.

toma visualized by an imaging technique will appear as a hypodense area. The most common symptoms of chronic subdural hematoma are gait disturbance, hemiparesis, headache, dementia, urinary incontinence and consciousness disturbance[1]. Our patient developed urinary incontinence, mental confusion, headache and gait disturbance. Her risk factors for chronic subdural hematoma included repeat episodes of gastroduodenal bleeding, long-standing antiaggregation therapy and infection. Bilateral hematomas and recurrent platelet aggregation reduction also suggested the possible development of thrombasthenia.

In general, acquired or hereditary pathologic bleeding can result from defects in the procoagulant mechanisms, defects in the mechanisms of hemostasis control, and abnormal fibrinolysis. Defects in procoagulant mechanisms may include platelet count or function abnormalities, coagulation factor defects, or vascular defects. Platelet function disorders include defects of platelet adhesion, aggregation and activation, secretion defects, signaling pathway defects, and defects in platelet size or membrane phospholipids. These may be inherited, or more commonly, acquired. Inherited defects are von Willebrand's disease and Bernard-Soulier syndrome (adhesion), Glanzmann thrombasthenia (aggregation) and Chédiak-Higashi syndrome (secretion defect). Our patient had normal platelet count and no signs of cardiovascular disease, therefore repeat tests occasionally indicating reduced platelet aggregability raised suspicion of Glanzmann thrombasthenia. Glanzmann thrombasthenia is an autosomal recessive syndrome with the incidence of 1 *per* million, and implies qualitative and quantitative abnormalities of the GpIIb/GpIIIa platelet membrane glycoprotein complex[8-12].

Acquired dysfunction is most commonly associated with antiaggregation agents that are currently widely and frequently unselectively used. There are many other drugs demonstrated to influence platelet

function, e.g., non-steroidal anti-inflammatory drugs (NSAIDs), thienopyridines, GPIIb/IIIa receptor antagonists, drugs that increase platelet cAMP, anticoagulant and fibrinolytic agents, cardiovascular drugs (nitrates, furosemide, angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers), cytostatics (danorubicin, mitomycin), psychiatric drugs (chlorpromazine, haloperidol) and antihistamines. Dual antiplatelet therapy with aspirin (acetylsalicylic acid, ASA) and thienopyridine (clopidogrel) is standard care after coronary stenting. Besides the use of ASA and clopidogrel, the use of nitrates, furosemide, ACEI and calcium channel blockers was also established by history data.

In a retrospective study of 123 patients with spontaneous subdural hematoma, 76% of patients were found to take aspirin (n=78) and warfarin (n=15), suggesting the use of aspirin to increase significantly the risk of cerebral hemorrhage and associated complications[13]. Clinical evidence for the efficacy of clopidogrel bisulfate relies on two double-blind studies, CURE and CAPRIE. The CURE study demonstrated the risk of myocardial infarction and stroke to be reduced, while the rate of gastrointestinal hemorrhage was 1.3%, of intracranial hemorrhage 0.1% and of fatal hemorrhage 0.2%[14-16].

The effect of ASA and clopidogrel on platelets lasts throughout the platelet life span, for about 7 days; therefore, in our patient platelet aggregation tests yielded abnormal results on admission. Later on, aggregation tests normalized due to transfused platelets and platelets formed *de novo* in the body. The addition of transfused platelets, post-hemorrhage reactive hypercoagulation, operative procedures (hyperfibrinogenemia, tissue thromboplastin release) and bed rest with venous stasis probably favored the development of iliac vein thrombosis on day 14 of craniotomy.

The complications of hemorrhage and chronic subdural hematoma call for due caution on the selection and follow up of patients prescribed antiaggregation agents. This in particular applies to elderly patients, where the risk of bleeding is already increased due to fragile capillaries, and in a very small but significant group of patients with inborn platelet function disorder. However, due to limited resources, testing for platelet aggregation cannot be routinely done prior to introducing antiaggregation therapy. Therefore, due attention should be paid to patients with a history of mucocutaneous bleeding, thrombosis or skin necrosis. Some new drugs like direct thrombin and Factor X inhibitors (dabigatran and rivaroxaban) have already passed phase III clinical trials on prophylaxis and prevention of venous thrombosis. These agents may completely replace warfarin and vitamin K antagonists in the treatment and prevention of venous thromboembolism because they require no activity monitoring or dose adjustment. For now, studies of their potential effects in the prevention of arterial thromboembolism are yet to be expected. Thus, due caution is still warranted on selecting patients prescribed antiaggregation agents, and their side effects should be strictly monitored.

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Sažetak

NETRAUMATSKI OBOSTRANI SUBDURALNI HEMATOM UZROKOVAN ANTIAGREGACIJSKOM TERAPIJOM: PRIKAZ SLUČAJA I PREGLED LITERATURE

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U 64-godišnje bolesnice koja je zbog ne-STEMI srčanog infarkta dobivala aspirin i klopidogrel razvio se netraumatski obostrani subduralni hematom praćen smušenošću, vrtoglavicom i glavoboljom. Kod prijma je utvrđena smanjena agregacija trombocita u ADP testu pa je kraniotomija i dekompresija odgođena za 4 dana. Četiri dana nakon prestanka uzimanja klopidogrela i aspirina te uz transfuziju od 12 doza trombocita prolazno se normalizirala agregabilnost trombocita pa je učinjena obostrana trepanacija i uklonjeni su hematomi. Slijedio je odličan neurološki oporavak. Smanjena agregabilnost trombocita bila je prisutna do 12. poslijeoperacijskog dana. Sumnja na Glanzmannovu trombasteniju isključena je protočnom citometrijom. Četrnaestoga poslijeoperacijskog dana nastala je tromboza desne femoralne vene koja je liječena smanjenim dozama heparina i varfarina. Uz prikaz bolesnice analizira se rizik od krvarenja i tromboze u bolesnika koji uzimaju antitrombocitne lijekove. Preporuča se oprez u starijih bolesnika kod kojih su prisutne i druge teške bolesti, što povećava rizik od krvarenja.

Ključne riječi: Ključne riječi: *Hematom, subduralni – dijagnostika; Hematom, subduralni – etiologija; Hematom, subduralni – terapija; Antikoagulansi – terapijska primjena; Progresija bolesti; Starija osoba; Prikaz slučaja*