

## A rare case of heparin-induced thrombocytopenia and cerebral venous sinus thrombosis with antiphospholipid syndrome and possible systemic lupus erythematosus

Rzadki przypadek małopłytkowości wywołanej przez heparynę i zakrzepicy zatok żylnych mózgu z zespołem antyfosfolipidowym i możliwym toczeniem rumieniowatym układowym

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### Abstract

Cerebral venous sinus thrombosis is a relatively rare type of stroke which can be complicated by intracerebral haemorrhage resulting often in poor prognosis. Antiphospholipid syndrome and systemic lupus erythematosus both have been associated with cerebral venous sinus thrombosis. Furthermore, a few cases combining heparin-induced thrombocytopenia with cerebral venous sinus thrombosis have been described in the literature. We present a 57-year-old female patient who was admitted reporting confusion and fever for 4 days. She was immobilized due to a thoracic vertebral fracture and received enoxaparin as a prophylaxis for deep venous thrombosis. A computed tomography scan demonstrated extensive cerebral venous sinus thrombosis and two ipsilateral haemorrhagic infarcts. Moreover, the patient was serum-positive for heparin-induced thrombocytopenia antibodies and had persistent fever. A thorough immunological and serological investigation turned out consistent with antiphospholipid syndrome with possible systemic lupus erythematosus. The patient was treated accordingly and was finally discharged one month later, afebrile, with mild neurological deficits.

**Keywords:** cerebral venous sinus thrombosis, intracerebral haemorrhage, heparin-induced thrombocytopenia, antiphospholipid syndrome, systemic lupus erythematosus

### Streszczenie

Zakrzepica zatok żylnych mózgu jest względnie rzadkim typem udaru mózgu, który może być powikłany krwotokiem śródmózgowym i często wiąże się ze złym rokowaniem. Zespół antyfosfolipidowy i toczeń rumieniowaty układowy to znane czynniki ryzyka wystąpienia zakrzepicy zatok żylnych mózgu. Ponadto w literaturze opisano kilka przypadków współwystępowania małopłytkowości wywołanej przez heparynę z zakrzepicą zatok żylnych mózgu. W pracy przedstawiono przypadek 57-letniej kobiety przyjętej do szpitala z objawami splątania i gorączką trwającymi od 4 dni. Pacjentka była unieruchomiona z powodu złamania kręgu piersiowego kręgosłupa i przyjmowała enoksaparynę w ramach profilaktyki zakrzepicy żył głębokich. Tomografia komputerowa ujawniła rozległą zakrzepicę zatok żylnych mózgu i dwa obszary udaru krwotocznego zlokalizowane w tej samej półkuli mózgu. U pacjentki stwierdzono również pozytywny wynik badania w kierunku przeciwciał w surowicy odpowiedzialnych za wystąpienie małopłytkowości wywołanej przez heparynę oraz uporczywą gorączkę. Dokładne badanie immunologiczne i serologiczne ujawniło obecność zespołu antyfosfolipidowego z możliwym toczeniem rumieniowatym układowym. Pacjentka została poddana odpowiedniemu leczeniu i wypisana z oddziału miesiąc później, bez gorączki oraz z łagodnymi deficytami neurologicznymi.

**Słowa kluczowe:** zakrzepica zatok żylnych mózgu, krwotok śródczaszkowy, małopłytkowość wywołana przez heparynę, zespół antyfosfolipidowy, toczeń rumieniowaty układowy

## INTRODUCTION

**C**erebral venous sinus thrombosis (CVST) is a relatively rare type of stroke, more often presenting in younger patients (Saposnik et al., 2011). The causes of CVST are multiple and diverse including genetic or acquired prothrombotic conditions (considering also the transient prothrombotic states of pregnancy and puerperium), systemic autoimmune diseases, infections, cancer, trauma and medications such as oral contraceptives. Intracerebral haemorrhage (ICH) is a serious complication of CVST, affecting about 30% of patients resulting often in poor prognosis (Fuentes et al., 2011). Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) have been associated with CVST and stroke (Kumral et al., 2012). A few cases combining heparin-induced thrombocytopenia (HIT) with CVST have been described in the literature (Fesler et al., 2011; Kyritsis et al., 1990; Meyer-Lindenberg et al., 1997; Tun et al., 2012; Warkentin and Bernstein, 2003) and there are also reports that relate HIT and APS, since both disorders are characterised by a specific antibody-mediated hypercoagulable state (Hoppensteadt and Walenga, 2008). The pathophysiological pathway that could connect the above situations is not well understood. We present a case of a 57-year-old woman who combined all the aforementioned clinical entities.

## CASE REPORT

A 57-year-old female patient was admitted to the Emergency Department (ED) reporting fever (38.8°C), intermittent confusional state and dysphasic alterations in both receptive and expressive language, starting 4 days earlier. She was immobilised for 9 days due to a traumatic thoracic vertebral fracture and was treated with low molecular weight heparin (LMWH) (enoxaparin) as a prophylaxis for deep vein thrombosis (DVT).

The medical history of the patient was significant for hypertension, osteoporosis, depression, longstanding severe migraine,  $\beta$ -thalassemia minor and infertility. Regarding the latter the patient had a history of two abortions and seven unsuccessful attempts of *in vitro* fertilization. The exact gestational age at the time of the abortions was not clarified exactly but it was during the first trimester of pregnancy. No clear evidence for previous use of any type of heparin was found in the patient's medical history.

The current medication of the patient was paroxetine and bromazepam for depression and an oral antihypertensive agent not registered in her medical record. She reported the use of a combination of ergotamine tartrate and caffeine (Cafergot) on a daily basis for 10 consecutive days prior to her admission, trying to relieve her migraine. She received no medication for osteoporosis during the last 2 years.

The neurological examination at the ED revealed fluctuating disorientation in time and space, global dysphasic symptoms more prominent to the motor speech component, an indifferent right plantar reflex and a possible minor deficit of the right visual field which could not be evaluated in detail due to the confusional/dysphasic state of the patient. No signs of meningism were present and fundoscopy was negative for papilloedema.

Blood tests and urgent imaging with a brain (computed tomography, CT) scan were performed.

The initial laboratory investigations displayed low platelet count (60,000/ $\mu$ L), low haematocrit (29.9%), elevated white blood cell count (11,100/ $\mu$ L – neutrophils: 76%), elevated C-reactive protein (121.2 mg/dL) and normal INR and aPTT. Blood and urine cultures were negative for infection. The urgent brain CT scan demonstrated two haemorrhagic infarcts in the left temporal lobe and the left cerebellar hemisphere (Fig. 1). Further investigation with an urgent CT venography revealed extensive left CVST.

Given the combination of low platelet count, CVST and the treatment with enoxaparin for at least 9 days before the admission, the possibility of HIT was potent. Taking into consideration that CVST is a severe and often fatal condition, the patient continued the anticoagulant treatment despite the haemorrhagic infarcts. Enoxaparin was replaced with fondaparinux which is one of the treatment choices for HIT (Kang et al., 2015). Despite the persistent fever and the elevated C-reactive protein, a lumbar puncture was not performed due to the anticoagulant treatment, the low platelet count and the haemorrhagic infarcts. A broad spectrum of intravenous antibiotics was administered, as an empiric treatment for possible respiratory, urinary or central nervous system infection.

Further investigations included virological, immunological and coagulation testing and screening for HIT antibodies. The results of the immunological testing showed high titre of anti-nuclear antibodies (ANAs 1/1,240) and positivity for lupus anticoagulant antibodies (LA1 and LA2) which remained positive after a mixing test. Furthermore, the screening test for serum HIT antibodies was positive. The findings were consistent with a diagnosis of HIT in a background of APS with possible SLE and the haematologist consultant suggested the initiation of dexamethasone.

Brain magnetic resonance imaging (MRI) with magnetic resonance angiography and magnetic resonance venography (MRV) was performed on the second day after the patient's admission and confirmed the initial findings showing haemorrhagic elements in the left temporal lobe, the left insula and basal ganglia, and the left side of the cerebellum. Mild oedema surrounded the haemorrhagic lesions. Thrombosis of the left sagittal and sigmoid venous sinuses and of the left internal jugular vein was observed (Fig. 2).

Three days after the initiation of dexamethasone, the platelet count started to increase gradually. A new CT scan was

performed 14 days after the admission and revealed partial absorption of the haemorrhagic lesions and decreased oedema.

The patient was discharged from the neurology department one month later with mild dysphasic symptoms and right hemianopia. Her discharge medication was acenocumarol and dexamethasone at a tapering dose schedule according to the haematologist's and rheumatologist's instructions.

The immunological tests were repeated 3 months later and showed again high titre of ANAs and positive LA1 and LA2 antibodies.

At 6 months follow-up, the patient presented ambulatory with improved speech. The MRI and MRV follow-up demonstrated significant improvement (Fig. 3). The patient is treated constantly with anticoagulants for the APS but she has not yet been under immunomodulatory medication for the SLE.

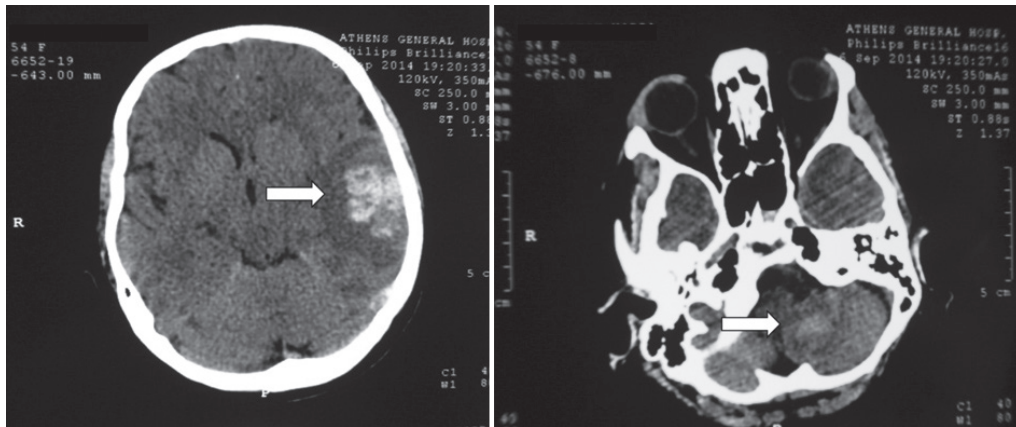


Fig. 1. Brain CT at presentation demonstrates haemorrhagic lesions at the left temporal-parietal lobe and left cerebellar hemisphere (white arrows)

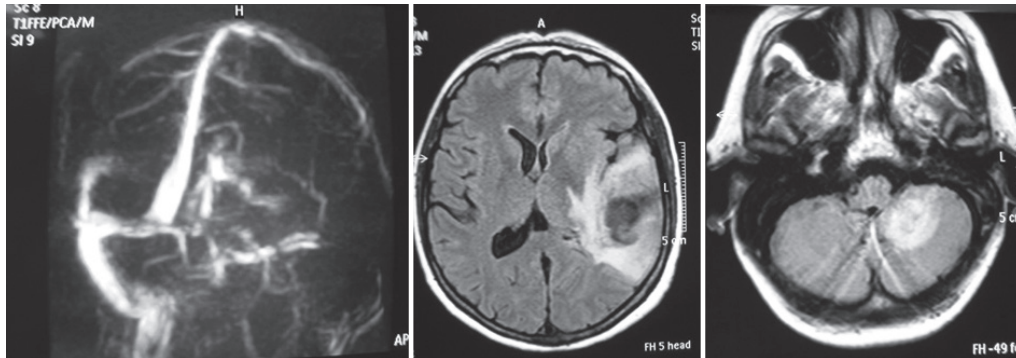


Fig. 2. MRI and MRV 2 days after admission. Thrombosis of the left sagittal and sigmoid venous sinuses and left internal jugular vein. Oedema surrounds the haemorrhagic lesions

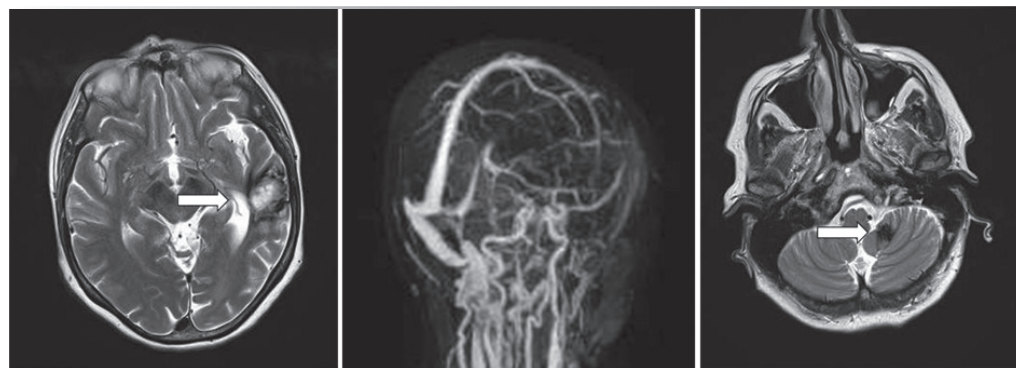


Fig. 3. Six months' follow-up MRI-MRV demonstrating chronic haemorrhagic lesions (white arrows). Improvement of flow at the left cerebellar venous sinuses

## DISCUSSION

The presented case is characterised by both diagnostic and therapeutic challenges.

Heparin-induced thrombocytopenia with thrombosis (HITT) is a life-threatening situation that requires immediate cessation of the causing factor and proper treatment mainly for prophylaxis for thrombotic events. HITT is usually caused by the administration of heparin for >5 days and is almost twice as frequent in female patients (Salter et al., 2016). However, it has also been reported even after a single dose of unfractionated heparin (Warkentin and Bernstein, 2003). In our case, CVST complicated by 2 haemorrhagic infarcts and low platelet count combined with the use of enoxaparin for at least 9 days prior to admission raised the possibility for a HITT diagnosis that was confirmed by laboratory testing. However, false positive or false negative HIT laboratory results are not rare and only the combination of clinical and laboratory evidence can support the diagnosis (Favaloro et al., 2017).

The diagnostic procedure became more complicated by the concurrent diagnosis of APS and the possible diagnosis of SLE. Both of these autoimmune disorders are independent factors for CVST and could explain, separately or together, the causal pathway for the CVST and the subsequent haemorrhagic infarcts (Saposnik et al., 2011). In our patient the APS diagnosis is supported by at least one laboratory (high titres of LA1 and LA2 persisting for more than 12 weeks) and one clinical criterion (thrombotic event which in our case is the CVST) according to the 2006 consensus statement (Miyakis et al., 2006). Thrombocytopenia could also be attributed to HIT or the possible SLE and was not considered for the APS diagnosis. The history of 2 abortions and infertility was also not taken into account due to the lack of details about the exact gestational age during the events. Although the American College of Rheumatology criteria for a definite diagnosis of lupus were not fulfilled, the thrombotic event coexistence with increased ANAs and LA1–2 and thrombocytopenia do not allow for an easy exclusion of an APS-SLE syndrome (1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus). The puzzle complicates further considering the discussion about the reported false positive tests for HIT in patients with APL and/or SLE (Pauzner et al., 2009). Despite the fact that the percentage of these false positive HIT tests is under debate (Alpert and Salmon, 2010), they definitely exist and, in our case, make the diagnostic approach even harder.

Treatment decisions for this patient were controversial. Anticoagulation was a necessity due to CVST but increased the risk of expansion of the ICH. The instructions from the American Heart Association/American Stroke Association support that CVST should be treated with anticoagulants despite the presence of ICH (Class IIa;

Level of Evidence B) (Saposnik et al., 2011), but diverging views suggest that the treatment should be individualised (Fuentes et al., 2011). The treatment decision to use fondaparinux, which according to the literature seems to be the safest LMWH for the treatment of HIT, allowed managing both CVST and HIT (Kang et al., 2015). On the other hand, fever with increased C-reactive protein and confusion implied a possible central nervous system infection, but a lumbar puncture was contraindicated because of the extent of ICH, the HIT-induced low platelet count and the anticoagulant therapy. The administration of broad spectrum antibiotics was mandatory at this point. When the laboratory results came up, a multidisciplinary meeting of neurologists, haematologists and rheumatologists assessed both the benefits and risks leading to the addition of dexamethasone as immunosuppression for both HIT and APL-SLE. While the patient was still in hospital the anticoagulant agent was shifted to acenocoumarol which was the patient's main discharge medication.

## CONCLUSION

There are only a small number of cases in the literature that combine either HIT and CVST or HIT and APS, but as far as we know a case that combines all the above conditions at presentation has never been described. An interesting case combining CVST, APS and HIT was described by Hsieh and his colleagues. In that case HIT was secondary to treatment with unfractionated heparin and LMWH for the pre-existing CVST (Hsieh et al., 2013). In addition, the majority of the cases reported usually did not have such a favourable outcome (Hoppensteadt and Walenga, 2008). We have presented here our treatment decisions upon an unclear entity with controversial treatment approaches, in an effort to provoke thoughts and suggestions for the better management of such complicated life-threatening conditions.

### Conflict of interest

*The authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the content of this publication and/or claim authorship rights to this publication.*

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