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Spontaneous spinal epidural haematoma: management and main risk factors in era of anticoagulant/antiplatelet treatment

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ABSTRACT

Aim of the study. Spontaneous spinal epidural haematomas (SSEH) are rare nosological units wherein acute collections of blood develop in the spinal canal. SSEH are usually manifested by sudden severe back pain accompanied by the development of neurological symptoms. In this study, we retrospectively describe management and the main risk factors of SSEH in a series of 14 cases.

Material and methods. Between 2010 and 2019, we examined 14 patients (age range 17–89 years, 10 women) diagnosed with SSEH. Eight cases were patients using anticoagulant therapies (six warfarin, one dabigatran, one apixaban) and two others were using ASA of 100 mg/day. The exact localisation and extent of changes was determined from acute magnetic resonance imaging. Three people using warfarin had INR values higher than 3.0 at the time of their diagnosis.

Results. Ten patients (71%) were taking oral anticoagulants or antiplatelet agents. In seven patients, SSEH were localised in the lower cervical/thoracic spine. Ten patients (71%) had arterial hypertension. Six patients underwent acute surgery due to rapidly developing spinal cord compression. Eight patients (57%) with slight or mild neurological symptoms were successfully managed without surgery.

Conclusions. SSEH should be suspected in any patient receiving anticoagulant/antiplatelet agents who complains of sudden, severe back pain accompanied by neurological symptoms. SSEH is mostly localised in the lower cervical/thoracic spine. Arterial hypertension appears to be a risk factor of SSEH. Early decompression is an important therapeutic approach; in cases with minor neurological deficits, conservative treatment may be chosen.

Key words: spontaneous spinal epidural haematoma, spinal cord compression, anticoagulant therapy, surgical and non-surgical management, warfarin

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Introduction

Spontaneous spinal epidural haematomas (SSEH) are rare nosological units concerning the expansion of blood collection in the spinal canal without clear traumatic or iatrogenic causes [1]. The incidence of SSEH is usually reported as 0.1/100,000 inhabitants [2, 3] and the male-to-female ratio is 1.4:1 [4]. Spontaneous spinal epidural haematomas cases have been detected more frequently with the wider availability of magnetic resonance imaging (MRI), which is the most important morphological method for SSEH detection [5].

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Anticoagulation and antiplatelet therapy are the commonest management option in various indications, especially in elderly patients. One important and rare complication of this therapy is SSEH [6–8]. This acute condition requires rapid diagnostics and therapeutic intervention. Surgical treatment remains the gold standard, especially in cases of progressive neurological deficit [9]. In minor haematomas associated with only slight neurological symptoms, it is possible to choose conservative management with detailed monitoring of neurological functions [7–10].

To date, SSEH has not been extensively studied in as large a population of patients as is presented in this study. We retrospectively studied a group of 14 patients who were diagnosed and treated in two hospitals between 2010 and 2019. We discuss the clinical symptoms of SSEH, diagnostic procedures, conservative and surgical treatments, and different risk factors.

Material and methods

Between 2010 and 2019, 14 patients (aged 17–89 years, 10 women) were hospitalised with spinal epidural haematomas in two large hospitals in the Czech Republic. Patients were taken from the database of the Departments of Neurology at University Hospital in Prague and University Hospital in Pardubice. Both these hospitals are public ones providing care to a local district with a population of more than 1 million inhabitants. Data was analysed from patients' medical histories and clinical reports from the intensive care unit, surgical and neurological departments. We analysed demographic data, risk factors with stress on anticoagulant/antiplatelet treatment, clinical and MRI findings, treatment approach, and clinical outcomes. Only such patients were included in this study who fulfilled the criteria of SSEH: no history of recent trauma, clinical picture of spinal lesion, and spinal MRI without evidence of bleeding source. If patients presented haematomas related to any type of trauma (mild, severe, iatrogenic, or therapy-connected), their data was not analysed. The Ethical Committees for both hospitals approved this retrospective study (EK-E/02/0/2020).

A common MRI protocol for spinal imaging was used in both hospitals, including T1 weighted, T2 weighted and fat suppressed T2 weighted sagittal sequences; T2 weighted or gradient T2* weighted axial sequences.

Apart from a detailed clinical neurological examination, we assessed the severity of spinal cord disability using the American Spinal Injury Association Impairment Scale (AIS) classification, where A corresponds to a complete spinal lesion and E is a normal finding [11]. AIS classification was extracted from components of the chart given at the beginning of the patient's complaints after the hospital admission.

Results

Table 1 sets out the demographic and clinical data, including MRI showing haematoma localisation, treatment efficacy, and risk factors with a focus on anticoagulant use.

Fourteen patients aged 17–89 years (median 67.5) with SSEH were finally included in this retrospective study. Most were older and aged 59–69 years (eight subjects, 57%), while two patients were young (17 and 42 years). Women accounted for 71% of the patients. The most frequent comorbidities were cardiovascular diseases (hypertension, atrial fibrillation, atherosclerosis, and deep vein thrombosis). Ten patients aged above 59 years suffered from arterial hypertension (71%). Six of them (60%) were treated by a combination of three antihypertensive drugs. Eight patients were taking oral anticoagulant therapy (six warfarin, one dabigatran, and one apixaban) and two patients were using ASA of 100 mg/day. In summary, 10 patients out of 14 (71%) were given oral anticoagulant/ /antiplatelet therapy. There was an increase of INR values above 3.0 in three patients using warfarin (two cases for atrial fibrillation, one for deep vein thrombosis). One of them (patient 5) had a history of the Valsalva manoeuvre having been performed in close proximity to the onset of the problems. One young patient was pregnant (week 36 + 6 days), and suffering from iron deficiency anaemia. Atrial fibrillation was present in six patients (46%), dyslipidaemia in three (21%), obesity (BMI above 30) in three (21%), deep vein thrombosis in two (14%), anaemia in two (14%), diabetes mellitus in one (7%), smoking in one (7%), rheumatoid arthritis in one (7%), and hypothyroidism in one (7%). Ten patients (71%) had two or more vascular risk factors. In addition, spondylogenic spinal stenosis was present in two patients, and two patients had old osteoporotic fractures at the level of SSEH.

All patients in this study reported acute onset of severe pain as the initial symptom, mostly in the lower cervical spine (eight subjects, 57%). Twelve patients reported some degree of neurological deficit accompanying the pain. Two patients (5 and 6) experienced urinary retention at the beginning of SSEH. Only two patients (3 and 7) did not develop any neurological deficit. The median time between clinical symptom onset and acute neurological assessment in a hospital was 4.5 hours (2–22 hours).

All patients underwent urgent magnetic resonance imaging for the detection of SSEH. The time interval between symptom onset and spinal cord MRI ranged from 5 to 26 hours, with a median of 12.5 hours. With respect to the affected level of the spine, the lower cervical/upper thoracic region was the most common site of involvement (seven subjects, 50%). Three patients had localisation in the middle thoracic spine, and four patients in the lower thoracic/upper lumbar level. Nine of our patients (64%) had SSEH in the posterior (dorsal) epidural space, four patients at the anterior (ventral) epidural space, and one had a combination of both.

Six patients (43%) underwent surgery (decompression, bilateral laminectomy) due to rapidly developing spinal cord compression (Fig. 1–3). The time interval between symptom onset and operation ranged from 7 to 28 hours, with a median of 16.5 hours. Before the surgery, frozen plasma was used in one patient (patient 10) to normalise INR. One patient (patient 13)

Table 1. Demographic and clinical data of SSEH group

Pt	Sex	Age	Comorbidities	Therapy (daily dose)	Anticoagulation/antiplatelet drugs	Clinical signs at onset	Clinical neurological status at onset	AIS at onset	Hours to admission	Hours to MRI	MRI – level of SSEH, other findings	Hours to surgery	Treatment	AIS final
1	M	59	HT, AF, BMI 26.4	Telmisartan 80 mg	Warfarin INR 3.2	Sudden local pain in low cervical spine, no irradiation	Hemiparesis with progression to quadriparesis and hypesthesia	C	6	12	C5-T1 ventral	18	Surgery: laminectomy C5-T1	E
2	F	68	HT, AF, dyslipidemia, BMI 31.7	Fenofibrate 200 mg, Telmisartan 40 mg, Amiodarone 200 mg, Atorvastatin 20 mg	Warfarin INR 2.4	Local pain in cervical region, no irradiation	Quadriparesthesis and transient quadriparesis	D	12	24	C1-C6 dorsal (4x3 cm), C1-C3 ventral (2x1 cm), spinal cervical spondylogenic stenosis	None	Conservative — analgesics	E
3	F	59	HT, AF, dyslipidemia, BMI 32.4	Telmisartan 40 mg, Amiloride 25mg, Hydrochlorothiazide 2.5 mg, Atorvastatin 20 mg	Warfarin INR 3.4	Pain in low cervical spine, no irradiation	Quadriparesthesis	D	5	8	C6-T1 dorsal, no spondylosis	None	Conservative — analgesics	E
4	F	68	HT, DM, smoking (20 /day), BMI 27.2	Betaxolol 20 mg, Nitrendipine 20 mg, Ramipril 5 mg	None	Pain in cervical--thoracic region with irradiation to occipital region	Slight right-sided hemiparesis	D	10	26	C3-T5 dorsal	None	Conservative — analgesics	E
5	F	64	HT, BMI 26.8, atherosclerosis, acute pancreatitis in history	Losartan 12,5 mg, Metoprolol 25 mg	ASA 100 mg/day	Sudden pain in thoracic region after Valsalva manoeuvre (sneezing) (12), no irradiation	At onset quadriplegia with anaesthesis and retention of urine	A	2	8	T6-T11 dorsal, spinal cervical spondylogenic stenosis, no myelopathy	None	Conservative — analgesics	E
6	M	89	HT, AF, BMI 26	Metoprolol 25 mg, Valsartan 160 mg, Furosemide 20 mg	Warfarin INR 2.8	Low back pain, no irradiation	Slight paraparesis with retention of urine	D	4	10	L1 ventral	None	Conservative — analgesics	E
7	F	84	HT, AF, RA, sick--sinus-syndrome (pacemaker MRI compatible), BMI 27.5	Methylprednisolone 4 mg, Metoprolol 25 mg, Furosemide 20 mg, Gabapentin 600 mg, Omeprazole 20 mg	Dabigatran 110 mg twice daily, normal plasmatic value of dabig<20 ug/l (HEMOCLOT)	Low back pain with irradiation to abdomen	Normal	E	6	20	T12-L1 ventral, size 15x6x3 mm, old osteoporotic fracture T12 and L1, spinal lumbar spondylogenic stenosis	None	Conservative — analgesics	E
8	M	89	HT, AF, CHF, anaemia, osteoporosis, depression, benign prostatic hyperplasia, BMI 25.1	Atenolol 100 mg, Furosemide 40 mg, Carvediol 25 mg, Finasteride 5 mg, Ginkgo biloba 80 mg, Sertraline 50 mg	None	Low back pain, no irradiation	Slight flaccid paraparesis, normal sensation	D	22	24	T12-L2 dorsal 18x11x8, old osteoporotic fracture of T9 and T10	None	Conservative — analgesics	E

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Table 1 cont. Demographic and clinical data of SSEH group

Pt	Sex	Age	Comorbidities	Therapy (daily dose)	Anticoagulation/antiplatelet drugs	Clinical signs at onset	Clinical neurological status at onset	AIS at onset	Hours to admission	Hours to MRI	MRI – level of SSEH, other findings	Hours to surgery	Treatment	AIS final
9	F	17	Gravidity (week 36+6), iron deficiency anaemia (Hb 72, Ery 3.23, MCV 74.3, HTC 0.24, Trombo 255), BMI 22.2	Ferrosi sulfas hydricus (34.5 mg Fe2+)	None (INR 0.9)	Pain in cervical--thoracic region for a week, no irradiation	Mild paraparesis more pronounced on left side, loss of sensation from T1	C	2	12	C7-T2 dorsal, no spinal stenosis	16	Surgery: Caesarean section, laminectomy T1-T2	D
10	F	67	Hypothyreosis, Leiden mutation (heterozygote), BMI 22.4	Levothyrosin 25 ug	Warfarin INR 5.2	Sudden onset of local pain in cervical-thoracic region	Mild motor paraparesis	C	1	18	T2-T6 dorsal, no spinal stenosis	28	Fresh frozen plasma, surgery: laminectomy at C7-T6	C
11	F	68	HT, DVT, total left hip endoprosthesis, chronic venous insufficiency, varicose veins, BMI 38.2	Metoprolol 25 mg, Valsartan 160 mg, Furosemide 20 mg	Warfarin INR 1.63	Pain with irradiation to left hip	Severe motor paraparesis	B	2	5	T11-L4 dorsal, no spinal stenosis	7	Surgery: laminectomy T11-L4	C
12	F	61	Low back pain, dyspepsia, BMI 27.7	Tramadol 100 mg, Esomeprasole 40 mg	None	Pain in low cervical spine with irradiation to right shoulder	Dysesthesia, hypestheisa on right hand with slight motor weakness of C7	D	12	16	C6-C7 ventral, no spinal stenosis	None	Conservative — analgesics	D
13	M	42	DVT, PE, tinnitus, dyspepsia, varicose veins, BMI 25.3	Pantoprazole 20 mg, Flavonoidorum 1500 mg	Apixaban 2x5 mg/day (Trombo, INR, aPTT normal)	Mild pain in cervical region with irradiation to both upper extremities	Mild to severe quadriparesis with hypesthesia from C7	C	2	10	C4-C7 dorsal, no spinal stenosis	11	Surgery: laminectomy C3-C7	D
14	F	77	HT, subrenal aortal aneurysm dyslipidemia, COPD, INR 1.1, Trombo 348, BMI 25.2	Felodipine 10 mg, Losartan 50 mg, Bisoprolol 2.5 mg, Atorvastatin 20 mg	ASA 100 mg/day	Sudden onset of pain in thoracic--lumbar region with irradiation to abdomen	Paraplegia with partial loss of sensation from T10	A	2	13	T9-T12 dorsal, no spinal stenosis	17	Surgery: laminectomy T9-L1	C

HT — hypertension; AF — atrial fibrillation; COPD — chronic obstructive pulmonary disease; PE — pulmonary embolism; DVT — deep vein thrombosis; DM — diabetes mellitus; CHF — chronic heart failure; RA — rheumatoid arthritis; ASA — acetylsalicylic acid; C — cervical; T — thoracic; INR — international normalised ratio; F — female; M — male; MRI — magnetic resonance imaging; BMI — body mass index; AIS — American Spinal Injury Association Impairment Scale. Only Patient 4 was smoking

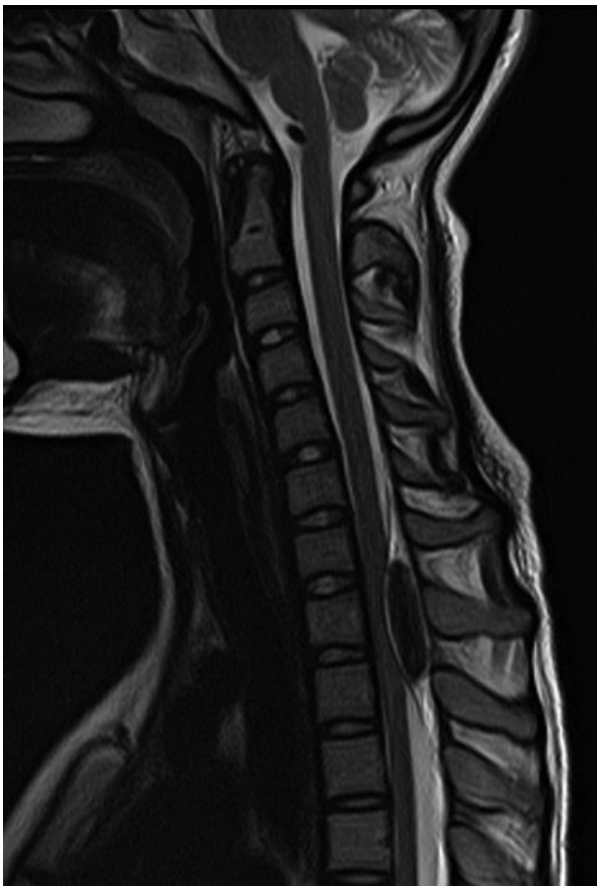

Figure 1. MRI of cervical/thoracic spine (sagittal T2W) performed after onset of symptoms shows expansive behaviour of extradural non-homogenic mass in posterior epidural space (patient 9)

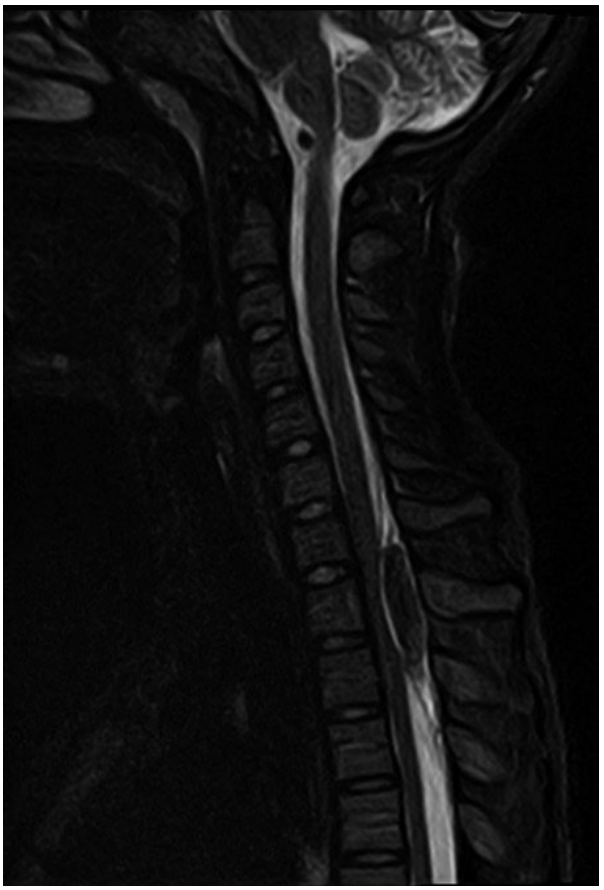

Figure 2. MRI of cervical/thoracic spine (sagittal STIR) shows same extradural mass localised dorsally with compression of spinal cord but without myelopathy (patient 9)

taking apixaban had normal coagulation in the blood. Patient 7 presented a normal plasmatic value of dabigatran in the blood (dabigatran was < 20 ug/l, proved by HEMOCLOT — trombin inhibitory assay). In three patients after surgical decompression, the clinical condition improved substantially. The clinical conditions of the other eight patients (57%) were more favourable and conservative approaches (symptomatic treatment with analgesics) along with detailed monitoring of neurological functions were chosen. Ten patients showed clinical improvement by more than one point on AIS classification. No patient developed clinical worsening. All patients underwent rehabilitation. Nine patients were able to walk without assistive devices (Patients 1–6, 9, 12, 13). One female patient (Patient 5) suffered from very severe neurological deficit (AIS A) at disease onset. This spontaneously improved very quickly and she refused surgery. She had a full clinical recovery within 24 hours. This case has already been published [12].

Discussion

Spontaneous spinal epidural haematoma (SSEH) is a rare entity, with the prognosis affected by the severity of spinal cord compression, a delayed final diagnosis, prompt surgical intervention, and a well-chosen conservative approach in spontaneously improving cases [8, 13]. In our study, one of the most important findings was that 71% of patients (mostly of older age) received oral anticoagulation/antiplatelet treatment and 57% of patients with slight or mild neurological symptoms were successfully treated with a conservative approach.

The cause of SSEH is usually a vessel rupture but the pathophysiology is not yet fully understood. The exact localisation of rupture and source of bleeding during surgery is mostly not identified [14]. Another important source of bleeding is the venous plexus in the epidural space [2, 3]. The reported cause of SSEH is a sharp increase in intra-abdominal or intra-thoracic pressure which is then transferred to the spinal vessels [12, 15].

The incidence of SSEH is bimodal in age and location. The age structure of SSEH patients has its first peaks between the ages of 15 and 20 and again between 67 and 70 [16, 17]; however, in our patient group most people were aged 59–69 years (eight subjects). The peaks of the location curve are the spinal levels of C6 and T12 [18]. In this study, the lower cervical/upper thoracic region was the most common site of

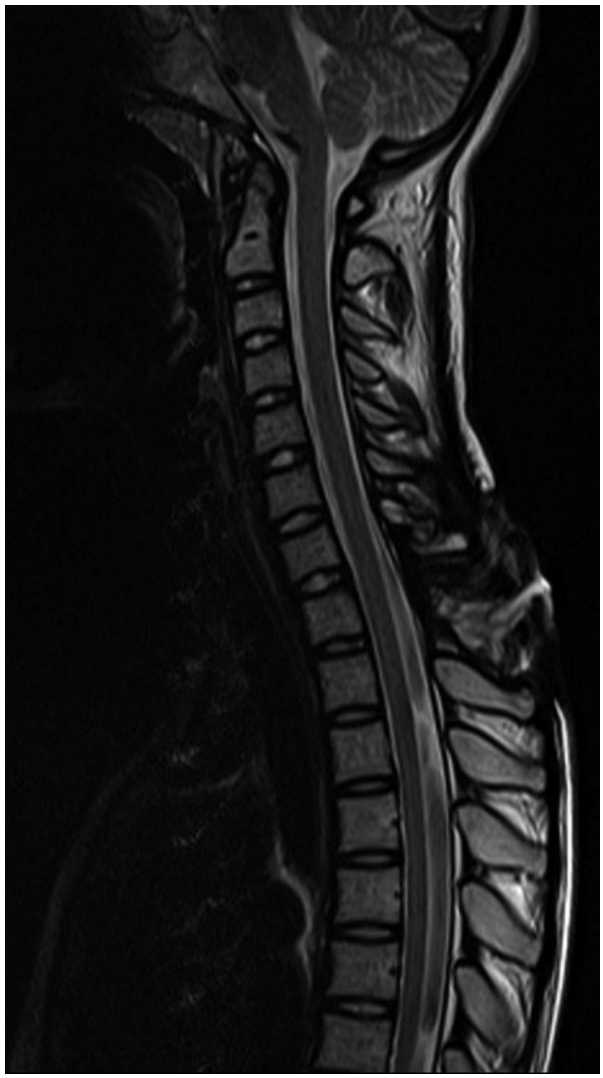

Figure 3. MRI of cervical/thoracic spine (sagittal T2W) performed after successful decompressive surgery with total removal of haematoma (12 days after onset of SSEH), showing only oedematous changes in posterior epidural space (patient 9)

involvement, followed by the lower thoracic/upper lumbar level. The posterior (dorsal) epidural space is affected most commonly due to its position relative to the spinal sac [3]. We observed similar findings where most of our patients (64%) had SSEH in the posterior epidural space.

The main risk factor for the development of SSEH is a coagulation disorder, either congenital (e.g. haemophilia) or iatrogenically induced (e.g. anticoagulation, antiplatelet therapy, haemodialysis) [13, 15, 19]. Anticoagulant therapy is used in thromboembolic diseases (acute phlebothrombosis and pulmonary embolism), in the treatment of atrial fibrillation, in pregnant women, in dialysis patients, and for many other indications. SSEH as a complication of anticoagulation treatment most often develops with the use of warfarin [20, 21], especially in patients who have an INR of above 3 [13]. There have been reports of patients with SSEH on direct oral anticoagulants (DOAC) such as dabigatran [22, 23], rivaroxaban [24, 25] and apixaban [26], but much less than in warfarin. Similar observations of SSEH development in patients with warfarin, dabigatran and rivaroxaban were found also in our study.

Other SSEH risks include atherosclerosis and arterial hypertension [13, 27–29], pregnancy [19], and deep diving [30]. In a population aged 65 to 74, the overall prevalence of hypertension was as high as 50% [31, 32] which was in concordance with our data. Antihypertensive treatment using three drugs in an elderly population was observed in 30% [31]. In contrast, we present a higher incidence (60%) of these patients in our study. Two patients presented old porotic fractures in proximity to SSEH. Recently, three unusual cases of spinal epidural haematoma occurred in senile patients affected by osteoporotic fractures [33].

The first clinical manifestation of SSEH is usually a sudden, sharp pain in the back accompanied immediately or after a slight delay by neurological symptoms caused by the compression of tissue structures located in the spinal canal [13, 24]. An early symptom of a growing haematoma is sometimes described as a stabbing, severe pain in the spine [16, 34]. Other neurological symptoms may gradually develop depending on the location of the haematoma – transverse spinal cord lesions, spinal cord hemisection, posterior spinal cord syndrome, conus medullaris and epiconus syndrome, cauda equina syndrome, different radicular syndromes, etc. [13]. The course of patients in our cohort corresponded to the above description but with varying severities and durations of disability. The hemiparesis in one patient progressed to quadruparesis; another patient reported subjective weakness of all limbs, which improved during her transport to the hospital via ambulance. Two patients experienced urinary retention at the beginning.

Magnetic resonance imaging of the spinal canal is the most important method in the diagnosis of SSEH: the haematoma appears as an expansive lesion; its signal changes over time mainly due to haemoglobin degradation, and fluid movement in the spinal canal can also cause actual changes of the haematoma's appearance. In the initial phase, an acute haematoma is isosignal in T1 weighted scans and hypersignal in T2 weighted scans. In the following days, the haematoma signal intensity can alternate in both sequences, but it typically increases in T1 weighted scans during days 3–5 [35]. Afterwards, in chronic haematoma, both T1 and T2 signal decrease due to haemosiderin formation. Loss of signal in T2* gradient sequence helps to differentiate haematoma from other expansive lesions; this phenomenon is caused by the presence of deoxyhaemoglobin and hemosiderin in acute and chronic haematoma, respectively [36]. The baseline MRI can also show spinal cord oedema or myelopathy; its presence is considered to be an unfavourable prognostic factor.

The treatment of SSEH depends on the severity and dynamics of the neurological symptoms [37]. Surgical management is indicated in patients with spinal cord involvement

according to the AIS scale A-C [11]; however, recently, we published a case report of SSEH after loud sneezing in a patient using antiplatelet therapy (100 mg ASA daily), where the initial paraplegia fully resolved spontaneously within 24 hours [12].

The mean length of SSEH with a conservative approach has been observed on MRI to be significantly longer compared to operated SSEH [17]. In this study, our results did not support this observation.

Due to the quick development of neurological symptoms, SSEH requires a multidisciplinary team and proper management, with 24/7 MRI availability and surgical decompression of the spinal cord. The prognosis of the patient depends on his/her level of disability before surgery and the speed of spinal cord decompression [13, 16, 34]. Surgery (usually laminectomy or hemilaminectomy) should be performed on incomplete lesions within 48 hours of the onset of symptoms [28, 38]. In our group, spinal cord decompression was performed 7–28 hours after SSEH depending on the development of clinical symptoms, and no patient reported a worsening of neurological deficit.

Conservative SSEH management is based on the elimination of risk factors and minimising the risk of further bleeding. Immediate interruption of anticoagulant therapy is recommended in the overuse of warfarin. Correction of the coagulation is improved by the administration of fresh frozen plasma, vitamin K or prothrombin complex concentrate. Idarucizumab, a specific antidote to dabigatran, has been successfully used in SSEH, resulting in a complete neurological recovery [23]. Adnexanet alpha is recommended to be used as an antidote for patients taking apixaban or rivaroxaban [39]. In our study, we used fresh frozen plasma only in one patient with an INR of above 3. Bed rest at the beginning and analgesic therapies are also recommended. Long-term monitoring of patients is necessary to detect the possible progression of the condition, thus enabling any indications of surgery early on.

Clinical implications/future directions

The commonest risk factors which can lead to SSEH are anticoagulant therapy (warfarin or direct oral anticoagulants) and intensively treated hypertension in triple combination. Other predisposing factors are antiplatelet therapy, anaemia, metabolic diseases (diabetes mellitus, hypothyroidism) and pregnancy.

SSEH is a rare disease but it should be considered in patients with acute spinal cord or radicular symptoms accompanied by a sudden sharp pain in the spine.

Approaches to treating SSEH must be individual, with careful monitoring of the patient's clinical condition and a responsible choice of treatment modalities, whether surgical or conservative. Severe neurological deficit at the beginning and/or rapid progression of the clinical neurological status are the most important observations leading to prompt surgical decompression of the spinal cord. We recommend being more conservative if moderate neurological deficit is present, especially in older people who have multiple chronic diseases, when the surgical approach may carry a higher risk.

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