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Case Report

Thrombosis in Iron Deficiency and Iron Deficiency Anemia: A Review of our Cases and the Relevant Literature

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Abstract

We evaluated our thrombosis cases for iron deficiency (ID) or iron deficiency anemia (IDA) retrospectively and reviewed the literature. We established that iron parameters were studied in 17 of 64 patients with thrombosis and 2 of 17 patients had IDA. Case 1 (age 16, female) had occlusions in sigmoid and transverse sinuses and right jugular vein and case 2 (age 15, male) had infarct in right cerebellar hemisphere. While case 1 additionally had mastoiditis, high Factor (F) VIII and PAI 4G/5G polymorphism, case 2 who underwent a recent aortic graft insertion operation for aortic aneurysm had high serum lipids, lipoprotein a, homocysteine, FVIII, d-dimer. Of 54 thrombosis cases with ID/IDA in the literature, cerebral thrombosis made up of 70.4% of all the cases, venous cerebral occlusions comprising 100% and 66% of venous thrombosis in children and adults respectively. Our findings show that ID/IDA may be a risk factor for thrombosis, especially in cerebral veins.

Keywords: Iron deficiency anemia; Coagulation; Thrombosis; Thromboembolism

Introduction

Many cases of thrombosis have been reported in both children and adults, associated with iron deficiency (ID) or ID anemia (IDA) so far [1-40]. Additionally, the frequency of severe anemia [1] or IDA [2] in adults with cerebral [1] or deep venous thrombosis with/without pulmonary embolism [2] were shown significantly higher than that of the healthy controls. We previously showed by thromboelastogram that children with IDA had a tendency to thrombosis [41]. Herein, we evaluated our patients with IDA and thromboembolism followed in our clinic and reviewed the relevant literature (Tables 1-3).

Materials and Methods

We examined the charts of our patients treated for thrombosis during 2013-2016 and had concomitant IDA/ID; additionally we studied the literature between 1972-2016, through 'Entrez-PubMed and Turkish Citation Index' databases, matching the key words 'thrombosis, thromboembolism, hypercoagulability; abnormal coagulation' with 'ID or IDA'

Results

Our search revealed that only 17 out of 64 patients with thrombosis diagnosed in our clinic during this period had been evaluated for iron parameters and only the 2 had IDA. These cases are presented below.

Case 1 (O.E.)

A 16-year-old girl was admitted due to headache, nausea, vomiting. She was diagnosed as otitis media (right) two weeks before and received antibiotics for seven days. A few days later, a continuous, blunt headache near right ear and right hemicranium propagating towards the right orbita developed which was accompanied by blurred vision, nausea and vomiting. Her physical examination revealed pallor, nasal discharge, bilateral papilledema and a systolic murmur of grade II/VI on the tract of right jugular vein. Cerebral magnetic resonance (MR) imaging (MRI) was compatible with mastoiditis and right jugular vein thrombosis. Cerebral MR venography revealed obliteration of the transverse

sinus and the right jugular vein at the sigmoid sinus level. She had increased Factor (F) VIII and plasminogen activator inhibitor (PAI) 4G/5G polymorphism and IDA. The other laboratory findings are presented in Table 1. She received antibiotics for six weeks, low molecular weight heparin (LMWH) for six months and oral iron for three months. The cerebral MRI, cerebral MR venography taken at the end of the 2nd month revealed normal. She had been well for 24 months of follow-up.

Case 2 (EA)

A 15 3/12-year-old boy was admitted to our clinic due to slight amnesia which developed 5 days after aortic graft insertion operation done for ascending aortic aneurysm. He was operated for aortic coarctation at 7 months of age. His physical examination revealed grade II/VI systolic murmur at the right 2nd intercostal space and little confusion in recalling the near past. The cerebral MRI and diffusion MRI revealed acute infarct in the right cerebellar hemisphere. The electroencephalogram (EEG) was normal. He had IDA, vitamin B12 (VB12) and folic acid deficiencies, elevation levels of homocysteine, FVIII, lipoprotein a, very light density lipoproteins, triglycerides, d-dimer, C-reactive protein (Table 1). He was started prednisolone, lansoprazole, acetylsalicylic acid, LMWH. Amnesia disappeared three days later. Iron and VB12 therapies were added after his condition stabilized. Anti thrombotic therapy was continued with LMWH for six months. He has been well for the 18 months of follow-up.

Table 1: Some characteristics of cases with thrombosis and iron deficiency anemia in our clinic.

Patient	Thrombosis	Age (y, mo) / Gender	Hb / MCV / SI / TIBC / TS / fer / thrombocyte count	Treatment / Last status	Radiologic Tests	Additional Tested Factors	Accompanying Systemic Disease/ Condition
O.E.	Right jugular vein, sigmoid and transverse sinus	17y, W	Hb: 7.65 / MCV: 59.1 / SI: 20 / TIBC: 409 / TS: 3 / fer: 2.6 / thromb: 320000*	LMWH, iron / Full recovery	Cerebral MRI: Inflammatory signals in the right mastoid cellules and signs of thrombus in the right jugular vein. Cerebral MR venography: Total obliteration of flow in the right jugular vein at the sigmoid sinus level and nearly total obliteration in the transverse sinus. Diffusion MRI: No acute infarct. Cerebral angiography: N Orbital MRI: N, Inner ear CT: N Carotid Doppler: N Chest X-ray: N Echocardiography: N. Temporal CT: Aeration of middle ear and mastoid bone Odiometry: N Impedance tests: N	PT, aPTT, TT, Pro C, Pro S, vWF, ATIII, FI, FV, VB12, homocysteine, d-dimer, FDP, FA, cholesterol, LDL, HDL, VLDL, lipoprotein a, C3, C4: N, ACA, APA, LA, ANA, anti DNA, PNH clone, Factor V Leiden, Prt G20210A, MHTFR C677T and A1298C mutations: (-) FVIII: %221 (High), CRP: 8.5mg/dl (High) PAI 4G/5G	Concomitant mastoiditis
E.A.	Right cerebellar hemisphere infarct (cranial MRI and diffusion MRI)	15y, M	Hb: 9.1 / MCV: 85.7 / SI: 45 / TIBC: 336 / TS: 11 / fer: 11.6 / thromb: 63600	LMWH, iron, VB12 / Low fat diet, /Full recovery		aPTT, TT, Pro C, Pro S, vWF, ATIII, FV, FDP, cholesterol, LDL, HDL, fibrinogen, C3, C4: N ACA, APA, LA, Anti DNA, PNH clone: (-),	Aortic coarctation, Ascending aortic aneurysm

						VLDL: 45 mg/dl (High), TG: 225 mg/dl (High), Lipoprotein a: 78.8 mg/dl (High), FA: 3.3 ng/ml (Low), VB12: 220 pg/ml (Low), D-dimer: 0,6 µg/ml (High), CRP: 101,9 mg/dl (High), F VIII: 207% (High), Pro C: 177% (High), Pro S: 150% (High), ANA:1/320 (+), Homocysteine: 16.49 µmol/L (High), Factor V Leiden, Prt G20210A, MHTFR C677T and A1298C: (-), PAI 5G/5G	

Abbreviations (Alphabetic order): ACA: Anti cardiolipin antibody; ANA: Antinuclear antibody; Anti -DNA: Anti deoxyribonucleic acid; APA: Antiphospholipid antibody; ATIII: Anti thrombin III; C3: Complement 3; C4: Complement 4; CRP: C-reactive protein; CT: Computerized tomography; F: Factor; FA: Folic acid; FDP: Fibrin degradation products; HDL: high density lipoprotein; H: High; LA: Lupus anticoagulant; LDL: low density lipoprotein; M: Male; MHTFR: Methylene tetrahydrofolate reductase enzyme; MRI: Magnetic resonance imaging; N: Normal; PAI-1: Plasminogen activator inhibitor-1; PNH: Paroxysmal nocturnal hemoglobinuria; Pro C: Protein C; Pro S: Protein S; Prt: Prothrombin; PT: Prothrombin time; aPTT: Activated thromboplastin time; TG: Triglyceride; TT: Thrombin time; VB12: Vitamin B12; VLDL: very low density lipoprotein; vWF: Von Willebrand factor; W: Woman

Literature Review

We established 54 cases with thrombosis and ID/IDA in the literature. The children and adults were almost equally affected (48.1% children, 51.8% adult), female/male ratio being 1.2 in children, 3.6 in adults. Veins were affected more than the arteries both in children and adults (73.1% and 53.6% respectively). Cerebral veins were occluded in 100% and 66.6% of the children and adults with thrombosis respectively. All the occluded non-cerebral veins in adults were retinal veins. The most common occluded arteries were the cerebral ones in children (85.7%) and non-cerebral arteries in adults (76.9%) mostly involving carotid artery (Tables 2 & 3). The rates of overall involvement of cerebral vessels in children and adults were 96.2% and 46.4% of all occlusions respectively (Tables 2 & 3). Nine out of 50 (18%) cases in the literature who were evaluated for other prothrombotic risk factors [3-15,17-40] had at least one risk factor like decreased protein S, Factor V Leiden, prothrombin G20210A mutations, increased Factor VIII, fibrinogen, lipoprotein a, cholesterol, anticardiolipin antibody, d-dimer, PAI, thrombin antithrombin complex levels and hemoglobin (Hb) S trait. Additionally four cases had patent foramen ovale.

Table 2: Characteristics of the patients in the literature who developed thrombosis and have underlying iron deficiency anemia.

Literature	Thrombosis	Age (y, mo) / Gender	Case Hb/MCV/SI/TIBC/TS/ fer/thrombocyte count/ others	Treatment/Last status	Additional Tested Factors	Accompanying systemic disease/ condition
BelmanAL et al. [4]	Straight sinus and the vein of Galen (hemorrhagic infarct in basal ganglia and thalami)	22 mo, M	Hb: 6 / MCV: 57 / SI:NA / TIBC: 427 / TS:NA/fer: 5 / throm: 540000; bone marrow: Iron stores absent	Dexamethasone, antibiotics, iron/ resolution at 5th mo.	RF, ANA: (-); Hb electrophoresis, ATIII, pr C, pr S, osmotic fragility, G6PD, PT, aPTT, Factor X, pyruvate kinase, bone scan: N	Left otitis media

Balcı K et al. [5]	Internal cerebral veins, vein of Galen, extension into inferior sagittal & left transverse sinus (Bilateral thalamic & basal ganglia defect)	38 y, W	Hb: 6.8 / MCV: 58 / SI: 22 / TIBC: NA/ TS: NA/ fer: 9.9 / throm:560000	LMWH, warfarin,erythrocyte transfusions, iron/Full recovery	Pr C, Pr S, ATIII, PT, aPTT, TT, Fibrinogen:N; ANA, anti ds DNA, APA, LA, ANCA: (-); CSF protein:Mildly high, tumor markers, abdominal USG, thoracic & abdomen CT, gynaecologic examinations: N	NA
	The veins of Galen & Rosenthal, extension into straight & left transverse sinus (Bilateral thalamic & basal ganglia defect)	18 y, W	Hb: 5.7 / MCV: 52.6 / SI: 42 / TIBC: NA / TS: NA / fer: 8.8, thromb:640000	LMWH, warfarin,erythrocyte transfusions, iron/Full recovery	PT, aPTT, TT, fibrinogen, ATIII, Pr C, Pr S, CSF protein: N; APA, LA: (-); abdominal USG, endoscopy, rectoscopy, gynaecological examinations: N	NA
Hartfield DS et al. [3]	Straight sinus, (Thalamic infarct)	18 mo, W	Hb: 6.7 / MCV:60 / SI: NA / TIBC: NA/ TS: NA/ fer: NA/ throm: 972000	Iron/ Full recovery	Screening tests including ANA: (-) (detail NA)	Gastroenteritis, history of recurrent otitis media
	Superior sagittal sinus	12 mo, W	Hb: 7.7 / MCV: 55 / SI: 2 / TIBC: 43; TS:<5% / fer: <5 / throm: 380000	Iron, dexamethasone, heparin, warfarin / Full recovery	Lipid profiles: N Metabolic screen: (-)	Gastroenteritis
	Cerebral artery Nonhemorrhagic infarct (basal ganglia/internal capsule)	11 mo, W	Hb: 12.6 / MCV: 78 / SI: 8 / TIBC: 57 / TS: 14% / fer: NA / throm: 693000	Iron, ASA/Full recovery	Metabolic screen: (-), small PFO	Recent upper respiratory tract infection
	Middle Cerebral Artery (Nonhemorrhagic infarct)	18 mo, W	Hb: 11.4 / MCV: 69 / SI: NA / TIBC: NA / TS: NA / fer: NA / throm: 373000	Iron/sequelae (seizure disorder)	NA	Recent gastroenteritis
	Superior Sagittal Sinus	6 mo, M	Hb: 4.5 / MCV: 54 / SI: 1 / TIBC: 61 / TS:% 2 / fer:<2 / throm: 657000	Iron, ASA /sequelae (seizure disorder, developmental delay)	Metabolic screen: (-)	Gastroenteritis (vomiting, fever)
	Middle Cerebral artery (Nonhemorrhagic infarct)	18 mo, W	Hb: 9.8 / MCV: 74 / SI: 9 / TIBC: 68 / TS: 13% / fer: NA / throm: 531000	Iron, ASA/Full recovery	Metabolic screen: (-)	Varicella course 3 weeks before

Kinoshita Y et al. [6]	Superior sagittal sinus; extention to transverse & sigmoid sinuses	14 y, M	Hb: 7.4 / MCV: 56.8 / SI: 9 /TIBC: 380 / TS:% 2 / fer: NA /throm: 289 000	Hydration, LMW dextran, warfarin, iron /recanalization but left sigmoid sinus remained occluded, vein of Labbe drained into left transverse sinus at 8th mo.	Pr C, ACA IgG, ATIII: N	Dehydration
	Superior sagittal sinus (hemorrhage in right temporal lobe, left parietal lobe/ right frontal lobe infarct)	47 y, M	Hb: 15.7 / MCV:78.1 / SI: 44 / TIBC: NA/TS: NA / fer: NA / throm: 276000	Hydration, heparin, warfarin, iron/ slight left hemiparesis at 2nd mo	Pr C, ACA IgG, ATIII: N	Dehydration, alcoholism
Sushil B et al.[7]	Internal cerebral vein, vein of Galen, straight sinus, sigmoid sinus & Rosenthal basal vein (bilateral hemorrhagic infarct of thalamus) (on 7th day of oral iron therapy)	9 mo, M	Hb: 4.1 / MCV: 48 / SI: 7 / TIBC: NA / TS: NA / fer: NA / throm: 866000	LMWH, continuation of iron /Partial recanalization at 3 mo.	Echocardiography, Hb electrophoresis, biochemistry, CRP, urine test: N Tests for prothrombotic disorder: (-) (details NA)	NA
Yokota H [8]	Superior sagittal sinus	37 y, W	Hb: 7.7 / MCV: 70.1 / SI:13 / UIBC: 286 /TS:NA / fer: 3.8/ throm: 356000	Hydration, heparin, warfarin, iron/full recovery at 2nd mo.	PT, CRP, thyroid functions, pr C, pr S, homocysteine, thoracic & abdominal CT, abdominal USG, upper GIS endoscopy: N; APA, ANA, AMA, LA: (-); Factor VIII: High; d-dimer, TAT: Slightly high	No
Corrales-Medina F et al.[9]	Vein of Galen, sinus rectus, left transverse sinus, left internal cerebral vein, jugular Φbulb	13 y, W	Hb: 5.1 / MCV: 63.6 / SI: NA / TIBC: NA / TS: NA / fer: 6 / throm: 483000	Heparin-warfarin / Full recovery of thrombosis but gliosis in centrum semiovale	Pr C & Pr S: Low (normalized later), other tests of hypercoagulability: N (details NA) Bleeding evaluation: N	Chronic menorrhagia

Lee JH et al. [10]	Right side transverse sinus and proximal sigmoid sinus (cerebellar infarction)	5y, M	Hb: 7.2 / MCV:NA/ SI: 54 / TIBC: 324 / TS: 14 / fer: NA/ throm: 130000	Iron, ASA, clopidogrel/full clinical recovery	Pr C, Pr S, ANA, LA, APA/ACA IgG/M , beta2 antibody IgG/M, thyroid functions, PNH tests: N	No
Ghosh PS et al. [11]	Superior sagittal sinus	19 mo, M	Hb:3.4/ MCV: NA/ SI:11 / TDBK: NA / TS: NA/fer: 16.4/ throm: 551000	Iron, LMWH/ residual non-occlusive thrombus at 3 mo	ACA IgG: High; ACA IgM: N; Pr C, Pr S, ATIII, Factor V Leiden: (-), Prt G20210A mutation: Heterozygote	No
	Inferior sagittal sinus	21 y, W	Hb: 8 / MCV:75/ SI: 14 / TIBC:NA/ TS:5 / fer: NA/ throm: 324000/Blood smear: Hypochromia, microcytosis	Heparin, warfarin, iron, asetazolamid / clinical & radiological improvement at 2nd mo.	Sedim, CRP, blood chemistry, thyroid functions, vitamin B12, folate, homocysteine, PT, aPTT, fibrinogen, Pr C, Pr S, ATIII, complement 3,4: N; Coombs tests, ANA, ACA, LA: (-); Lipoprotein a: High; Factor V Leiden, MTHFR C677T, Prt G20210 mutations: (-)	No
Roshal et al [13]	Left common carotid artery	41 y, M	Hb:8.9/MCV:59.6/SI: 14/ TIBC:480/ TS:3%/fer:2.1/ thromb:355000/Blood smear: Hypochromia, microcytosis	Heparin, warfarin, iron, ASA/minimal residual thrombus at 3 mo	PT, PTT, Pro C, Pro S, ATIII, FVIII, chemistry panels, rheumatological panels, HbA1C, urine drug screen, protein electrophoresis, EKG, chest X-ray: N; TEE: Small PFO; lower extremity venous Doppler, pelvic MR venography, abdominopelvic CT: N Prt G20210A, Factor V Leiden, MHTFR mutation, ACA IgG/M/A, LA, anti-beta 2 glycoprotein IgG/M/A: (-)	Past history of rectal bleeding

Saxena K et al. [14]	Bilateral atrial thrombus/ right middle cerebral artery, then right anterior cerebral artery (under heparin therapy); Bilateral pulmonary artery	4 y, W	Hb: 5.8 / MCV < 50 / SI: NA / TIBC: NA / TS: NA / fer: NA / throm: 748000	Rehydration, transfusion, entubation, heparin, fosphenytoin/ Brain death, exitus	Factor V Leiden (heterozygous);Prt G20210 A heterozygous; MTHFR 677C / T heterozygous; APA IgG: High; ATIII and homocysteine: N	Acute gastrointestinal hemorrhage, compensated shock
Ogata T et al. [15]	Superior sagittal sinus and cortical veins	55 y, M	Hb: 8.7 / SI 18 / TIBC: 522 / TS: 3.4 / fer: 13.3 / throm: 272000	Phenytoin, iron, ulcer treatment / Recanalization of sagittal sinus at 4th week	D-dimer and TAT: High PT,aPTT,fibrinogen, Pr C, Pr S, ATIII, CRP, serum protein constituents: N, ANA, ANCA, proteinase3: LA, ACA, anti-β2 glycoprotein I: (-);CSF: N, Endoscopy: Stomach, duedonum ulcers; chest, abdominal CT, scintigraphy: N	Peptic ulcer bleeding
Akins PT et al. [17]	Right internal carotid artery (in the bulb)	44 y, W	Hb: 6.6 / MCV:56.6/ SI: < 10 / TIBC: 399 / TS: <3%/ fer: < 10 / Tr: 666000	Blood transfusions, oxygen, ASA, heparin, iron / Full recovery	Biochemistry, chest x-ray, lower extremity Doppler, PT, aPTT, Pr C, Pr S, ATIII, TSH, Hb electrophoresis: N; ANA, ACA, PNH: -, TEE: PFO	Menorrhagia
	Right internal carotid artery (right parietal infarct)	20 y, W	Hb: 6.3 / MCV: 54,5 / SI: < 10 / TIBC: 355 /TS:3%/ fer: < 10 / throm:544000	Phenytoin, heparin, ASA, iron, blood transfusion /residual left upper-extremity clumsiness	Hb electrophoresis, sedim, PT, PTT, Pr C, Pr S, ATIII, lower extremity Doppler, ventilation/ perfusion scanning: N; ACA, ANA, LA, PNH, syphilis serologies: (-); TEE: PFO	Migraine
	Left common carotid artery	39 y, W	Hb: 7.1 / MCV: 62.9 / SI: 20, TIBC: 404 / TS:5% / fer: < 10 / throm: 652000	Blood transfusion, iron, warfarin, insulin, leuprolide acetate/Recovery	Hb electrophoresis, sedim, PT, aPTT, Pr C, Pr S, ATIII, ACA, ANA, PNH, syphilis serologies: (-); glucose & cholesterol: High	Menorrhagia (leiyomyoma)

Imai E et al.[18]	Left branch retinal artery	32 y, M	Hb: 6.4 /MCV:71,1/ SI:10 / TIBC:539 /TS:1.8%/ fer: 5.2 / throm: 252000	Stellate ganglion block, hyperbaric oxygen, iron/partial improvement in visual acuity at 4th mo	RF, ANA: (-); sedim, blood chemistry, aPTT, ATIII, fibrinogen, hepaplastin test, thrombo test: N; d-dimer: slightly high; echocardiography, chest x-ray, neck USG, brain and orbita CT:N	No
Kirkham TH et al. [19]	Left central retinal vein	44 y, W	Hb: 6.2/ MCV: NA / SI: 30/ TIBC: NA / TS: NA / fer: NA / throm: 280000 Blood smear: Marked hypochromia, anisocytosis, poikilocytosis; Bone marrow: No stainable iron	Blood transfusion, iron/fundus normalized, visual acuity 6/5	PT, kaolin cephalin time, fibrinogen, blood chemistry, urine analysis: N; ANA: (-); Radiology of oesophagus, stomach, small & large intestine: N; bone marrow biopsy: No stainable iron	Retinal hemorrhage
Kacer B et al. [20]	Left central retinal vein	37 y, W	Hb: 9.4 / MCV:74.2/ SI:15/ TIBC: 528/ TS:NA / fer:3 / throm: Normal (numeric value NA)	Heparin, tPA, iron/ visual acuity recovered	PT, PTT, ATIII, Pr C, Pr S, FI, FII, FVII, FVIII, FXII, vWF Ag, RistCoF, heparin Cofactor II, homocysteine, tPA, PAI, histidine-rich glycoprotein, CRP, sedim, viral serology: N; LA, ACA: (-)	No
	Right central retinal vein	50 y, W	Hb: 7.3 / MCV: 62/ SI: 10/ TIBC: NA / TS: NA / fer: <5 / throm: 390000	Heparin, steroid/ No response to treatment	NA	Hypermenorrhea
Nagai T [21]	Central retinal vein	29 y, W	Hb: 4.5 / MCV: 55 / SI: 5 / TIBC: 535 / TS: NA / fer: 4 / throm: 1020000	Iron/gradual improvement	Bone marrow: Increased megakaryocytes, normal karyotype	Myoma uteri
Matsuoka Y et al. [22]	Left central retinal artery	13 y, W	Hb: 5.5/ MCV: 60/ SI: 45/ TIBC: 450/ TS: NA / fer: 18/ throm: 534000	Urokinase, iron/good visual acuity	BUN, electrolites, plasma proteins, viscosity, glucose, lipids, urinalysis, chest X-ray, sedim, EKG, brain CT, orbit CT, neck USG, abdominal USG: N	No

Shibuya Y et al. [23]	Left central retinal vein	21 y, W	Hb: 6.5 / MCV: 66.4/ SI: 44/ TDBK:529/ TS: NA / fer: NA / throm: NA	Iron/visual acuity improved	NA	Anorexia nervosa
Knizley H &Noyes WD [24]	Transient ischemic attack (bilateral papilledema and right hemiparesis)	42 y, M	Hb: 5.1 / MCV: NA / SI: 43/ TDBK:548/ TS:8/ fer: NA / throm: 1015 000 Blood smear: Hypochromia, target cells	Iron/paresis & papilledema resolved within 72 hours & 2 mo respectively	Sickle cell preparation, stool hematest: (-); Hb A, clotting time, urinalysis, creatinin, glucose, chest&skull X-rays, brain scan, EKG, upper GIS series & small bowel, barium enema: N; proctosigmoidoscopy: internal hemorrhoids	Bronchial asthma, congenital clubbing of fingers/toes
Alexander MB [25]	Cerebrovascular accident (Right hemiparesis, aphasia, but cranial CT: N)	42 y,W	Hb: NA/ MCV: 62/ SI:19/ TIBC: 595 / TS: 3 / fer: 8 / throm: 1736000	Heparin,dextran, ASA, iron/resolution	Hb S, Coombs' tests, fibrinogen, fibrin split products, ANA: (-); bone marrow aspirate: Increased cellularity with increased megakaryocytes	Menorrhagia
Heller DS et al. [26]	Left middle cerebral artery (on 4th postoperative day (massive infarct of left cerebral hemisphere)	26 y, W	Hb: 9.8 / MCV: 77.6/ SI: NA / TIBC: NA / TS: NA / fer: NA / throm: 786000/ blood smear: Hypochromic, microcytic erythrocytes	Iron, mannitol, dexamethasone, intubation/death on postoperative 13th day	PT, PTT, fibrin split products: N, fibrinogen: probably high (515); autopsy: No vegetations, no septal defects; spleen: myeloid metaplasia; marrow: Increased megakaryocytes, erythroid and myeloid precursors, no stainable iron, minimally increased reticulin	Multiple myomectomies, ovarian endometriosis; incipient myeloproliferative disorder
Boon IS et al. [27]	Left transverse sinus	18 y, M	Hb: 7.4/ MCV: NA / SI: NA / TIBC: NA / TS: NA / fer: NA / throm: NA (studies confirming iron deficiency)	LMWH, iron/ Headache improved at discharge (follow-up NA)	APA &ACA: (-) Hb electrophoresis: sickle cell trait; retroviral & autoimmune screens: (-); ova, parasites, cysts on stool: (-) Factor VII: Low	NA
Nishiola K et al. [28]	Superior sagittal sinus, left transverse sinus	47 y,W	Hb: 7.6/ MCV: NA / SI: NA / TIBC: NA / TS: NA / fer: NA / throm: NA	Heparin, warfarin, antiplatelet drugs, iron/ clinical improvement; sustained disturbance in occluded veins; collaterals at 2nd year	CSF: increased cell counts and protein; d-dimer, CA-125: High	Pelvic adenomyosis

Raso S et al.[29]	Abdominal aorta (multiple infarctions of the spleen and the left kidney)	42 y,W	Hb: NA/ MCV:NA, / SI: NA / TIBC: NA / TS:NA / fer: 4/ throm: 1 133 000 After 2 weeks: Hb:8.2 / MCV:60.2 / SI: NA / TIBC: NA / TS:NA / fer:NA/ throm: 932000	Heparin, ASA, iron/ Complete recovery at 3rd mo	Inflammation markers, protein electrophoresis, coagulation profile, oncological markers: N; JAK-2,calreticulin, MPL mutations Factor V Leiden, Prt mutation (-); autoimmunity markers: (-)	Gastroesophageal reflux disease; diverticular, hemorrhoidal disease in colon
Nicastro Net al. [30]	Superior sagittal sinus, left sigmoid / transverse sinus, cortical vein thrombosis & bilateral pulmonary embolism (massive left frontotemporal hemorrhagic infarction	63 y, W	Hb:3,4 / MCV: NA / SI:1 / TIBC: NA / TS: NA / fer:2 / throm: NA	Blood transfusion, heparin, acenocoumarol/ almost complete recovery at 1st mo	Lower extremity Doppler, VB12, folate, protein electrophoresis: N; Factor V Leiden, Prt mutation, activated Pr C resistance, APA: (-); GIS endoscopies, mammography, endovaginal echocardiography, thorax+abdomen+pelvic CT: N	Vegetarianism
Habis A et al. [31]	Superior sagittal sinus thrombosis, extension into proximal left transverse sinus	18mo, M	Hb: NA / MCV: NA / SI:low / TIBC:high / TS: NA / fer:low / throm: NA (numeric values NA)	LMWH/ continued resolution of thrombosis at 6th mo.	PT, INR, PTT, Pr C, Pr S, ATIII, homocysteine: N, ACA, LA: (-) MTHFR mutation (type NA), Factor V Leiden: (-)	Meckel diverticulum
Bukarovich IF et al. [32]	Descending thoracal aorta (mobile thrombus); Right external iliac artery, proximal to midsuperficial femoral arteries, bilateral profundafemoralis arteries, right hypogastric, popliteal & anterior tibial arteries	42 y, W	Hb:7.7 / MCV:65 / SI: NA / TIBC: NA / TS: NA / fer: 9 / throm: 465000	Heparin, warfarin, iron/ resolution at 4th week	ATIII, homocysteine, Pr C:N; PAI-1: High; ACA IgM/IgG, LA:(-); Pr S: Mildly low Prt G20210A, Factor V Leiden: (-); EKG, echocardiogram, upper & lower GIS endoscopy, gynecologic evaluation: N	Menorrhagia
	Aortic arch (Mobile thrombus; cerebral infarct	49 y,W	Hb:8.4/ MCV:68/ SI:20/ TIBC:NA / TS:NA/fer:15/ throm: 567000	Heparin, warfarin, iron/ neurological status improved within 10 days	ATIII, homocysteine, Pr C, Pr S, PAI-1: N ACA IgM/IgG, LA: (-) Prt G20210A: (-), Factor V Leiden: (-), Echocardiography: N except thrombus in aortic arch, no GIS bleeding; gynecological evaluation: N	Menorrhagia

Benedict S et al [33]	Straight sinus and internal serebral veins	27 mo,W	Hb:7/ MCV:45 / SI: NA / TIBC: 408 / TS:NA / fer:<2/ throm:248000	Thrombectomy, heparin, warfarin, blood transfusion, iron/mild residual left hemiparesis	Hb electrophoresis: Hb E:%20.9; Pro C, Pro S, homocysteine, fibrinojen, FVIII:N; FV Leiden, anticardiolipin antibodies, ATIII, ANA: (-)	Fever & headache of 10 days previously
	Venous thrombosis in lateral ventricles	9 mo, W	Hb:6.6/ MCV:56.6/ SI:2/ TIBC:267/ TS:1/ fer<2 / throm:586000	Heparin, blood transfusion, iron/ sequelae (seizure disorder, spastic quadriparesis, static encephalopathy, hydrocephalus, visual impairment)	Pro C, Pro S, homocysteine, ATIII: N; FV Leiden, Prt G20210A mutation, anticardiolipin antibodies, lupus anticoagulant: (-)	Common cold & gastroenteritis previously
	Straight sinus and internal cerebral veins (hemorrhage in the posterior limb of the left internal capsule, & edema bilaterally in the basal ganglia and thalami)	19 mo, M	Hb:6.9, MCV:50 / SI:54 / TIBC:NA / TS: NA / fer: NA / throm:408000	Urokinase, heparin, dexamethasone, blood transfusion, iron/normal except slight tremor in upper extremities	Hb electrophoresis, Pro C,Pro S, ATIII, homocysteine, plasminogen:N; FV Leiden, Prt 20210 mutations; anticardiolipin antibo dies: (-)	Mild cough & vomiting for 2 days, before presentation
Munot P et al. [34]	Right middle cerebral artery (territory infarct)	14 mo, W	Hb:2.5 / MCV: 64/ SI: NA/ TIBC: NA / TS: NA / fer:13 / throm:376000	ASA, iron/ MRA normalized, but severe left hemiparesis persisted	Pr C, Pr S, ATIII, plasminogen, activated protein C ratio, Hb electrophoresis:N; Factor V Leiden, MTHFR-PT20210 mutations, ACA, LA: (-)	No
	Superior sagittal sinus, transverse sinus, frontal cortical veins (Bilateral frontoparietal venous infarcts)	35 mo, M	Hb:5.6 / MCV:53 / SI: NA/ TIBC: NA/fer: NA/ throm:257000	Transfusion, LMWH, warfarin, iron /No sequelae after 1 year	Pr C, Pr S, ATIII, plasminogen, activated protein C ratio, Hb electrophoresis:N; Factor V Leiden, MTHFR-Prt 20210 mutations, ACA, LA: (-); infection screen of CSF: (-)	Upper respiratory tract infection, sphenoid sinus opacification
	Internal cerebral veins, straight sinus and vein of Galen (diffuse cerebral swelling, hydrocephalus)	2 y, M	Hb:4.7 / MCV:54 / SI:8 / TIBC:- / TS: NA / fer:35 / throm:1744000	Heparin, warfarin, iron/ mild dystonic left hemiparesis after 1 year	Pr C, Pr S, ATIII, plasminogen, activated protein C ratio:N; Factor V Leiden, MTHFR-PT20210 mutations, ACA, LA: (-); Hb electrophoresis:Sickle cell trait	No

	Posterior segment of superior sagittal sinus, torcula, left transverse sinus and internal jugular vein	40 mo, M	Hb:7.7 / MCV:54 / SI: NA / TIBC: NA / TS: NA / fer:5 / throm: 250000	LMWH, warfarin, iron/Full recovery	Pr C, Pr S, ATIII, plasminogen, activated protein C ratio, Hb electrophoresis:N; Factor V Leiden, MTHFR, Prt G20210A mutations, ACA, LA: (-); infection screen of CSF: (-)	Left otitis media
Caglayan B et al [35]	Left internal carotid artery bifurcation	41y, W	Hb:7.5 / MCV:58 / SI:12 / TIBC:427 / TS: 2.8 / fer:12 / throm: 450000	Iron, heparin, warfarin/ resolution of thrombus	Pr C, Pr S, ATIII, fibrinojen, homocysteine, VB12, folate, PT, aPTT, LDL, HDL, echocardiogram:N; antiphospholipid antibodies, ANA, anti DNA, ANCA: (-)	Menorrhagia
Nakamizo T et al [36]	Thrombi in left ventricle and right int carotid artery , occlusion in right MCA	45y,W	Hb:6/ MCV:65,3 / SI:19 / TIBC:497 / TS:3.8/ fer:1.6 / throm:573000	ASA, clopigodrel, argatroban, iron/ resolution of thrombus	Pr C, Pr S, ATIII: N; antiphospholipid antibodies: (-)	Menorrhagia
Steble G et al [37]	Superior sagittal sinus	46y,M	NA (it is only said that he had 'iron deficiency anemia')	Heparin/recovery	NA	Rectum prolapse
Ready WK & Lowry NJ [38]	İnfarction in the left thalamus and right hypothalamus (angiography NA)	27 mo, W	Hb:4.5/ MCV:50.2/ SI:NA/ TIBC:NA / TS: NA/ fer: NA/ throm:728000; peripheral blood smear: signs of IDA	NA/ slow, incomplete recovery (cerebral palsy)	Serum chemistry: Mild hypoproteinemia, hypoalbuminemia, PT, aPTT, Hb electrophoresis N; Serum lead, ammonia: N; CarboxyHb: (-)	Diarrhea, vomiting, fever
Meena AK et al [39]	Superior sagittal sinus	4y,M	Hb:8.3 MCV: NA / SI: NA / TIBC: NA / TS: NA / fer:1.6 / throm:1194000	Heparin, acitrom, iron/steady improvement	Anti cardiolipin antibodies (-), collagen vascular disease profile, Pro C, Pro S, ATIII, PT, aPTT, FDP, fibrinogen, total cho, LDL:N, HDL:High	Nephrotic syndrome, papilloedema
Aoki N & Sakai T [40]	Superior sagittal sinus (hemorrhagic infarct)	48y, W	Hb:6.8 MCV:NA / SI:54 / TIBC:NA / TS: NA / fer: NA / throm:125000		PT, aPTT, FDP, fibrinogen: N	Mild papilloedema Myoma uteri
	Left transverse sinus (hemorrhagic infarct)	45y, W	Hb:5.9 MCV: NA / SI:NA / TIBC: NA / TS:NA / fer: NA / throm:171000		Coagulation studies & blood chemistry: N (details NA)	.Myoma uteri

Abbreviations (Alphabetic order): ACA: Anti cardiolipin antibody, Abbreviations (Alphabetic order): ACA: Anti cardiolipin antibody, AMA: Anti-mitochondrial antibody, ANA: Antinuclear antibody, ANCA: Anti neutrophil cytoplasmic, antibody, Anti ds DNA: Anti deoxyribonucleic acid, ASA: acetylsalicylic acid, APA: Antiphospholipid antibody, ANCA: Antineutrophil cytoplasmic antibody, aPTT: Activated partial thromboplastin time, ATIII: Anti-thrombin III, CA-125: Cancer antigen 125, CRP: C-reactive protein, CSF: Cerebrospinal fluid, CT: Computerized tomography, ECG:Electrocardiogram, F: Factor , FDP: Fibrin degradation products, fer: Ferritin, G6PD: Glucose-6-Phosphate Dehydrogenase; HDL: High-density lipoprotein, Hb: Hemoglobin (g/dl), IDA: Iron deficiency anemia, INR: International normalized ratio, JAK-2: Janus kinase 2, LA: Lupus anticoagulant ; LDL: Low-density lipoprotein, LMWH: low molecular weight heparin, M: Male, MCV: Mean corpuscular volume, MHTFR: Methylene tetrahydrofolate reductase enzyme; MPL: Thrombopoietin receptor, MRA: Magnetic resonance angiography, MRI: magnetic resonans imaging, N: Normal, NA: Not available, PAI-1: Plasminogen activator inhibitor-1, PFO: Patent foramen ovale, PNH: Paroxysmal nocturnal

hemoglobinuria, Pr C: Protein C, Pr S: Protein Santigen, PT: Prothrombin time, Prt: Prothrombin; RF: Rheumatoid factor, RistCoF: Ristocetin co factor, Sedim: Erythrocyte sedimentation rate, SI: Serum iron (µg/dl), tPA: Tissue plasminogen activator, TAT: Thrombin Antithrombin Complex, throm: thrombocytes, TIBC: Total iron binding capacity (µg/dl), TEE:Transesophageal echocardiogram, TS: Transferrin saturation(%) TSH: Thyroid stimulating hormone, TT: Thrombin time, UIBC: Unsaturated iron binding capacity, USG: Ultrasonography, VB12: Vitamin B12, vWF A: von Willebrand factor antigen, W: women.

Table 3: Characteristics of 54 patients in the literature developing thrombosis on the basis of iron deficiency anemia (Summary).

Age group	Age (median)	Gender (F/M/T)°	Total thrombosis attacks (n,%)			Venous (n,%)			Arterial (n,%)			Total thrombosis attacks (n,%)	
			Venous (n,%)	Arterial (n,%)	Total (n,%)	Cerebral (n, %)	Non cerebral (n, %)	Total (n,%)	Cerebral (n, %)	Non cerebral (n, %)	Total (n, %)	Cerebral thrombosis (venous+ arterial)	Total
Children	23 mo	14F/12M/26	19 (73.1 %)	7 -26.90%	26 (100%)	19 (100 %)	0 (0%)	19 (100%)	6x (85.7%)	1* (14,3 %)	7 (100 %)	25 -96.20%	26 (100 %)
Adults	504 mo (42y)	22F/6M/28	15 (53.6 %)	13 -46.40%	28 (100%)	10 (66.6 %)	5** (33.3%)	15 -100%	3 (23.1%)	10*** (76.9 %)	13 -100 %	13 -46.40%	28 -100%
All	228 mo (19y)	36F/18M/54	34 -62.90 %	20 (37%)	54 (100%)	29 (85.3 %)	5 (14.7%)	34 -100%	9 (45%)	11 (55 %)	20 -100 %	38 -70.30%	54 -100%

° : Female/Male/Total; ˣ1/6 had a coexistent thrombus in the atrium, *Thrombosis of retinal artery, **All are thrombosis of retinal vein, ***6/10 are thrombosis of carotid artery, one of them being coexistent with another thrombosis in the ventricle, 3/10 are thrombosis of aorta, 1/10 is thrombosis of retinal artery

Forty one out of 54 cases (75.9%) had at least one associated condition like infections (n:13), menorrhagia (n:10), gastrointestinal disorder like diverticulosis, rectal prolapsus, hemorrhoids (n:3), gastrointestinal hemorrhage (n:3), myoma uteri (n:3), dehydratation (n:2), oncologic problems like adenomyosis, endometriosis and myeloid metaplasia (n:2), papilledema (n:2), anorexia nervosa (n:1), nephrotic syndrome (n:1), migraine (1), retinal hemorrhage (n:1), bronchial asthma (n:1), alcoholism (n:1) (Table 2). All the 13 cases with concomitant infection were children all of whom had cerebral vessel occlusions, the majority involving the cerebral veins (n:9). The six had gastroenteritis, the three had otitis media, and the rest had various infections [3-15, 17-40] (Table 2).

Discussion

In this study, we presented two patients with cerebral thrombosis and IDA that were followed in our clinic and reviewed the literature. Of the 54 thrombosis cases with ID/IDA in the literature, cerebral thrombosis made up of 70.4% of all the cases, venous cerebral occlusions comprising 100% and 66% of venous thrombosis in children and adults respectively. Our report highlights the importance of prevention and early treatment of ID/IDA, especially in children. That, the frequency of ID/IDA in our patients with thrombosis (11.8%, Table 2) was lower than that in the literature (15-29%) [42] may be related to limited number of cases in our cohort. Our first case emphasizes the importance of preceeding/concomitant otitis media or mastoiditis as prothrombotic risk factors which were reported to accompany 24-62% of cerebral sinovenous thrombosis cases in children, among various infections [43]. The role of reactive thrombocytosis in the pathogenesis of thrombosis in ID/IDA is controversial [5,7,8,44,45]. However, the reduced cell deformability caused by microcytosis in ID/IDA causes hypercoagulation [3,7,45] through increasing blood viscosity and disrupting the normal blood flow pattern [3]. Concomitant dehydration, metabolic stress and infections increase metabolic demand of tissues, especially those of the basal ganglia, thalamus, hypothalamus [3,45], leading to anemic hypoxia and therefore venous thrombosis [7]. Endothelial damage develops [46-48] due to increase in oxidants [49] and reduction of antioxidants [49-53, 54] in ID/IDA, although controversial results are also available [55] and because of turbulant flow, which is a result of vasodilation and increased blood viscosity [17], thereby stimulating thrombocyte aggregation and thrombosis. However the effect of IDA on thrombocyte aggregation is controversial [46,56,57]. On the other hand, increased plasminogen activator inhibitor [58] was also reported. Whether clotting time is shortened and coagulation factors are increased like in other disorders like hemodilution [58], hemorrhagic shock [59] require further studies.

The idea that ID/IDA is a predisposing factor for thrombosis is relatively new. Our recent study with thromboelastography showed that IDA patients had a tendency to hypercoagulation [41]. That none of these patients had developed thrombosis suggested that additional thrombophilia factors may be required for development of thrombosis. The accompaniment of additional prothrombotic risk factors in our patients and those in the literature, although in various rates, support this hypothesis. Indeed, Stolz et al. showed that severe anemia is an independent risk factor for cerebral venous

thrombosis only when it is together with hypercholesterolemia and thrombophilia [1]. The main limitation of our study is that iron parameters were considered as prerequisite prothrombotic factors to be evaluated only after 2014 in our clinic; so only 17 cases could be evaluated. Incomplete search of additional prothrombotic risk factors of the cases in the literature are the limitations of the literature review.

Conclusion

Iron deficiency anemia or ID is a prothrombotic factor, as reported previously [60,61]. Two of our cases and 54 cases in the literature revealed coexistence of ID/IDA and thrombosis. Involvement of cerebral vessels in the majority of cases in childhood is striking. Further investigations are required to evaluate the role of additional prothrombotic risk factors in thrombosis that develops in ID/IDA patients.

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