

“Case Series: Ischemic Stroke Associated with Hypercoagulability in Individuals with Severe Anorexia Nervosa.”

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Case report

Keywords: Anorexia nervosa, Ischemic stroke, Dehydration, Hypoperfusion, Arteriosclerosis, Hypercoagulability, Case report

Posted Date: December 7th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-117909/v1>

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Version of Record: A version of this preprint was published on March 20th, 2021. See the published version at <https://doi.org/10.1186/s40337-021-00393-w>.

Abstract

Background

Numerous reports have indicated that patients with anorexia nervosa (AN) are at a relatively high risk of developing vascular diseases, including cardiovascular events and venous thromboembolism. However, there have been no previous reports of the development of ischemic stroke during refeeding therapy in patients with severe AN. This report is aimed at reporting the characteristics of an ischemic stroke in patients with AN.

Case presentations

Our study cohort consisted of 29 admission cases (19 patients), who received thorough medical, neurological and psychiatric examinations. Two patients were diagnosed as having developed ischemic stroke; the first patient showed multiple asymptomatic infarctions in the brain, while the second showed symptomatic focal infarction. Our findings suggest that dehydration and arteriosclerosis, in association with severe malnutrition, could predispose to the development of ischemic stroke in patients with severe AN.

Conclusions

Development of ischemic stroke in patients with AN might be overlooked. Our case series suggest that dehydration and arteriosclerosis, in association with severe malnutrition, may predispose to the development of ischemic stroke in patients with severe AN. Watching out for neurological signs would help in early diagnosis of ischemic stroke in patients with AN.

Background

Anorexia nervosa (AN) is a life-threatening psychosomatic condition, in which patients frequently develop severe complications, including hepatic dysfunction(1), gastrointestinal problems(2), respiratory failure(3), and cardiac disease(4). Some complications eventually lead to fatal despite careful treatments(5).

As for the vascular complications in patients with AN, these patients are at an elevated risk of developing cardiac events due to early arteriosclerotic damage(6). In addition, recent case series have suggested that the development of venous thromboembolism is often overlooked in patients with severe AN(7). Taken together, these previous reports suggest that patients with severe AN frequently have arteriosclerotic damage and venous stasis. Therefore, it is important to suspect vascular diseases, both arterial and venous, so that these complications would be diagnosed early and treated promptly.

In general, the causes of ischemic stroke are classified under four categories: atherosclerosis, cardiac embolism, small vessel disease, and others(8). Considering the high risk of vascular diseases in patients with AN, we can assume that patients with severe AN would also have a high risk of developing ischemic

stroke. However, to the best of our knowledge, there have been no published reports of patients with AN presenting with an ischemic stroke.

For this study, all admitted 29 cases with severe AN who needed emergent nutritional therapy and were admitted to our hospital between April 2018 and November 2020 were reviewed, and two of these patients developed ischemic stroke during their hospital stay.

This first report of two cases aims to draw attention to the high risk of development of ischemic stroke in patients with severe AN, because our cases showed only subtle neurological deficits. Clinicians need to watch carefully for the development of any neurological symptoms, including hemiplegia and linguistic impairment, in patients with severe AN receiving refeeding therapy, because these symptoms can sometimes be overlooked in clinical settings.

Case Presentation

Patient 1

Patient was a 31-year-old woman with a 10-year history of the binge eating/purging type of AN. She had no past history of neurological or cardiovascular diseases. She was a current smoker, with a smoking history of one pack-year. She was admitted to our hospital with a history of easy fatigability and immobility. She was unable to walk without assistance; however, her consciousness was clear, and examination revealed no signs of paralysis. We diagnosed her as having severe malnutrition, as her body mass index (BMI) was 8.8. Refeeding therapy was initiated at 2000 kcal/day with adequate electrolyte supplementation, during which she showed no complications; the electrolyte levels remained under good control, along with normal blood glucose levels. Water intake was restricted to 1 ml/1 kcal, and there were no complications such as congestive heart failure. On the 10th hospital day, she developed dysesthesia on her left shoulder. The Barre and Mingazzini test revealed left-sided hemiplegia, but her neurological symptoms resolved spontaneously within 10 minutes. Her vital signs were as follows: HR 74/min, BP 86/53 mm Hg, BT 36.7°C. Brain magnetic resonance imaging (MRI) revealed disseminated infarctions in the cortex bilaterally; however, her motor symptoms were not explained by the imaging findings (Figure 1). We diagnosed her as having had a transient ischemic attack, with incidental detection of multiple asymptomatic infarctions. Extensive clinical workup to determine the etiology of ischemia revealed that she had no systemic atherosclerosis or any source of embolism. However, her ankle-brachial index (ABI) and cardio-ankle vascular index (CAVI) values were elevated (Table 1), suggesting that she had arteriosclerotic damage without atherosclerosis. Laboratory tests performed on the day that she was diagnosed as having a stroke excluded common causes of early-onset ischemic stroke (vasculitis, dissection, moyamoya disease, antiphospholipid antibody syndrome). Elevated BUN/Cr levels suggested that she had dehydration, and the elevated serum levels of thrombin-antithrombin complex (TAT-III), platelet factor 4 (PF4), and β -thromboglobulin (β TG) indicated that she was in a hypercoagulable state (Table 1). She was started on aspirin 100 mg per day for secondary prevention. After the refeeding

therapy, she was discharged, and developed no recurrence of the ischemic attack during the subsequent two-year follow-up period.

Table 1
Laboratory data (Patient 1, 2).

		Pt 1	Pt 2	Reference value
Biochemistry	BUN (mg/dL)	13.3	23.3	8-20
	Cre (mg/dL)	0.32	0.55	0.46-0.79
	BUN/Cre	41.56	42.36	
	TC (mg/dL)	155	212	142-248
	TG (mg/dL)	58	71	30-117
	HDL-C (mg/dL)	65	82	48-103
	LDL-C (mg/dL)	81	122	65-163
	FT3 (pg/mL)	2.24	2.05	1.88-3.18
	FT4 (ng/dL)	0.74	0.72	0.7-1.4
	TSH (μIU/mL)	1.18	1.24	0.35-4.94
	Hb-A1c (%)	5.8	6.2	4.9-6.0
	BNP (pg/mL)	143.2	NA	0-18.41
	Coagulation profile	PT-INR	1.14	0.99
APTT (sec)		24.6	23.3	23.5-31.5
D-dimer (μg/mL)		1.2	1.7	0-1
TAT III (ng/L)		26.9	3.6	0-3
Protein C activity (%)		57	97	64-146
Protein S (%)		84	120	60-150
PF4 (ng/mL)		33	24	0-20
βTG (ng/mL)		104	105	0-50
Autoimmune antibodies	ANA	20	<20	<20
	PR3-ANCA (U/mL)	<1.0	<1.0	0-3.5
	MPO-ANCA (U/mL)	<1.0	<1.0	0-3.5
	Anti-cardiolipin antibody (U/mL)	<10	8	0-10
Imaging findings	Ultrasound (carotid artery)	no atherosclerosis	no atherosclerosis	

	Ultrasound (lower extremity veins)	no embolism	no embolism	
	Whole-body CT	no evidence of malignancy	no evidence of malignancy	
	Holter ECG	no evidence of Af	no evidence of Af	
	Echocardiography	EF 70%	EF 70%	
		Wall motion normal	Wall motion normal	
		No embolism	No embolism	
CAVI/ABI	CAVI (R/L)	7.8/7.7	7.1/6.9	
	ABI (R/L)	0.77/0.83	1.04/1.05	
CSF	CSF cell count (/μL)	NA	1	0-5
	CSF protein (mg/dL)	NA	24	15-45
	CSF IgG-index	NA	0.19	0-0.7
	CSF MBP	NA	negative	negative
	CSF OCB	NA	negative	negative

Patient 2

Patient was a 50-year-old woman with a 13-year history of the binge eating/purging type of AN. She had no past history of neurological or cardiovascular diseases. She was diagnosed as having severe malnutrition and hospitalized, as her BMI was 10.4; she was transferred to our hospital on the 18th hospital day for further nutritional therapy. Her vital signs were as follows: HR 103/min, BP 88/65 mm Hg, BT 37.0°C. On admission, she had difficulty in speaking and word comprehension, as a result of phonological errors and word-sound deafness, respectively. Her speech production concerning articulation was fluent. She, however, sometimes had word-finding difficulties along with phonological errors. Due to the phonological dysfunction, she sometimes stuttered and repeated the initial letter of a word. Brain MRI revealed a high-intensity area in the white matter of the left temporal-parietal lobe, underlying the left supramarginal gyrus as well as the left transverse temporal gyrus (Figure 2), which explained her phonological errors and word-sound deafness, respectively. We diagnosed her as having symptomatic cerebral infarction. Extensive clinical workup and laboratory tests performed to determine the etiology of the ischemia on the day that she was diagnosed as having a stroke revealed that she had no systemic atherosclerosis, no source of embolism, or none of the common causes of early-onset ischemic stroke, just like in patient 1. Also, like patient 1, she showed elevated levels of TAT III, βTG, and PF4, suggesting that she was in a hypercoagulable state (Table 1). Unlike patient 1, however, she showed no elevation of the CAVI or ABI value. On the other, she also showed elevated BUN/Cre levels, suggestive

of dehydration. The patient was therefore initiated on aspirin 100 mg daily for secondary prevention. Refeeding therapy at 1800 kcal/day and water restriction to 1 ml/1 kcal was successful, and after an uneventful course without the development of any complications, the patient was discharged while showing gradual improvement of her linguistic functions. A year later, she had a generalized convulsion due to the ischemic stroke, and the convulsions were well controlled with levetiracetam at the dose of 1000 mg per day during the subsequent follow-up period of a year. Her mild word-finding difficulties and word-sound deafness had almost disappeared.

Discussion And Conclusions

From this case series, we report two patients with severe AN who presented with ischemic stroke associated with a hypercoagulable state. These cases provide novel insights: clinicians should suspect development of ischemic stroke in patients with severe AN receiving intensive care, and specific approaches such as rehydration would be required in AN patients with an ischemic stroke.

First of all, our case reports suggest that patients with severe AN are at a higher risk of developing ischemic stroke than the general population. Based on the estimated annual incidence of juvenile (age 15-49 years) stroke of 10.8/100 000 (range 8.4 to 13.0) and men being at a higher risk than women(9), the incidence rate in our cohort (2/19) seemed to be higher than that in the general population. Our cases suggest that careful management, especially in the presence of neurological deficits, is needed for patients with severe AN.

In general, dehydration is thought to be involved in the occurrence of ischemia. Some researchers have suggested that dehydration may be an independent risk factor for in-hospital/postoperative ischemic stroke(10)(11). Moreover, dehydration combined with low blood pressures seems to induce cerebral hypoperfusion, which can exacerbate ischemic stroke(12). Our cases presented here showed high values of the BUN/Cre ratio (approximately 40) associated with a low blood pressure, suggesting that dehydration was the primary pathophysiologic mechanism underlying the development of ischemic stroke. However, there are currently no consensus diagnostic criteria for dehydration in patients with stroke. The BUN/Cre ratio is the most commonly used laboratory marker of dehydration(12); meanwhile, the BUN/Cre may overestimate dehydration in patients with AN, due to the decreased muscle volume(13). The values of BUN were nearly within normal range in our cases, indicating that other possible mechanisms might also exist. According to previous reports, dehydration was associated with a poor prognosis and functional outcome after acute ischemic stroke(14), and early rehydration therapy during acute ischemic stroke could improve the prognosis and the functional outcome(15). However, we were unable to apply these findings to patients with AN, since congestive heart failure is a common complication associated with refeeding syndrome(4). In our cases, water restriction to 1 ml/1 kcal was well tolerated, without the development of any cardiac complications. Rehydration therapy with careful monitoring is necessary, and further studies are warranted to establish the prevalence of dehydration and design a rehydration protocol for acute ischemic stroke in patients with severe AN.

In our presented cases, the elevated levels of β TG4/PF4 and TAT reflected increased platelet activation and thrombin formation, respectively, indicating that lacunar infarction was unlikely in our patients, since lacunar infarction is not known to be associated with a hypercoagulable state(16–18). Our extensive workup to determine the etiology of the cerebral infarction revealed no source of embolism. Based on these profiles, this case report suggests that ischemic stroke in cases of severe AN seems to be caused by arteriosclerosis. In fact, patient 1 might have had arteriosclerosis, because her CAVI and ABI were elevated. A previous report indicated that patients with AN had an increased platelet distribution width (PDW; an index of platelet size heterogeneity), suggestive of dysregulated thrombopoiesis(19). There have been no studies on the relationships between the PDW and ischemic stroke; however, a significant association has been reported between increased PDW and a high risk of myocardial infarction, suggesting that increased PDW may induce arteriosclerosis(20). As for dysfunction of the coagulation system, little has been reported on parameters of the coagulation profile, especially the plasma levels of thrombin, in patients with AN. Our cases presented here suggest that severe AN patients have systemic arteriosclerosis due to impaired platelet function and coagulopathy, which is consistent with previous reports(6,7).

The relationships among dehydration, arteriosclerosis, and severe malnutrition are quite complex. As described above, undernourishment in association with severe AN may induce hypoperfusion due to dehydration and arteriosclerosis in association with platelet dysfunction. On the other hand, hypovolemia caused by dehydration can elevate the plasma aldosterone level, which has been linked to vascular stiffening(21), and dehydration itself may be associated with cardiovascular disease through impaired endothelial function(22). These ideas are summarized in Figure 2.

This case report includes several limitations. First of all, this study was conducted at a single general hospital. Multicenter studies are warranted to establish the best treatments for ischemic stroke in patients with AN. Second, not all patients included in our cohort had undergone MRI assessments, because of insufficient equipment. Third, ischemic stroke secondary to paradoxical embolism could not be excluded, because transesophageal echocardiography was not performed in the patients; however, we consider it as having been unlikely as our patients showed relatively low serum D-dimer levels.

In conclusion, we report here two patients with severe AN with ischemic stroke caused by hypoperfusion and partial arteriosclerosis associated with severe malnutrition. Our extensive clinical workup to determine the etiology of ischemia just revealed a hypercoagulable state, without any apparent embolic or atheromatous source. Further extensive group studies or group-based studies are needed to elucidate the etiology of ischemic stroke in patients with severe AN.

Abbreviations

AN: Anorexia nervosa

BMI: Body mass index

TAT-III: Thrombin-antithrombin complex

PF4: Platelet factor 4

β TG: β -thromboglobulin

ABI: Ankle-brachial index (ABI)

CAVI: Cardio-ankle vascular index (CAVI)

BUN: Blood urea nitrogen

Cre: Creatinine

TC: Total cholesterol

TG: Triglyceride

HDL-C: High density lipoprotein cholesterol

LDL-C: Low density lipoprotein cholesterol

BNP: Brain natriuretic peptide

PT-INR: Prothrombin time international normalized ratio

APTT: Activated partial thromboplastin time

ANA: Anti-nuclear antibody

PR3: Proteinase 3

MPO: Myeloperoxidase

ANCA: Anti-neutrophil cytoplasmic antibody

ECG: Electrocardiogram

EF: Ejection fraction

Af: Arterial fibrillation

CSF: Cerebrospinal fluid

MBP: Myelin basic protein

OCB: Oligoclonal band

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patients for publication of this report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

YM has received a fellowship grants from Eisai and Grant-in-Aid for Young Scientists (KAKENHI) from the Promotion of Science within the past three years.

MM has received research support from Japan Society for the Promotion of Science and grants or speaker's honoraria from Daiichi Sankyo, Dainippon-Sumitomo Pharma, Eisai, Eli Lilly, Fuji Film RI Pharma, Janssen Pharmaceutical, Mochida Pharmaceutical, MSD, Nippon Chemipher, Novartis Pharma, Ono Yakuhin, Otsuka Pharmaceutical, Pfizer, Takeda Yakuhin, Tsumura, and Yoshitomi Yakuhin within the past three years.

Funding

Not applicable.

Author's contribution

YM acquired case data and drafted the manuscript. YS, HO, SK, SK and TT acquired case data. MF and MM supervised the study and substantively revised the manuscript. All authors read and approved the final manuscript.

Acknowledgments

None.

References

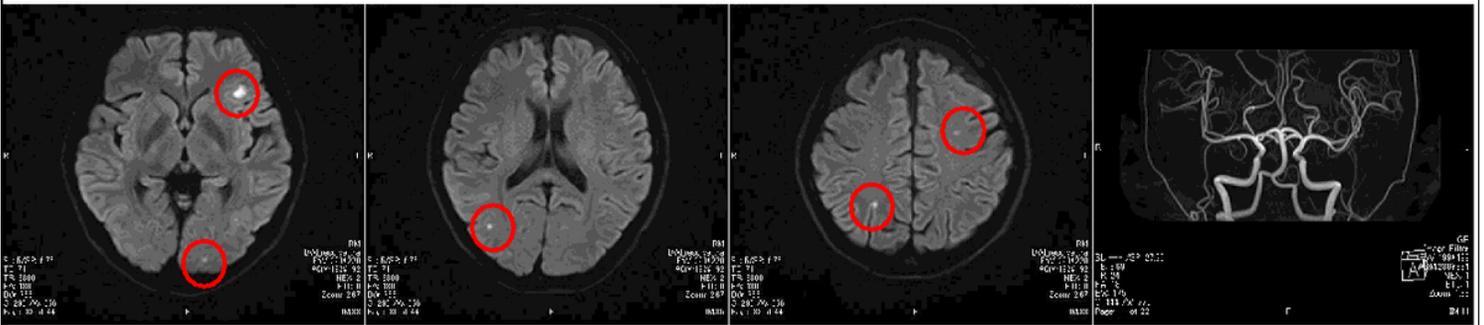
1. Rosen E, Bakshi N, Watters A, Rosen HR, Mehler PS. Hepatic Complications of Anorexia Nervosa. *Dig Dis Sci nov.* 2017;62(11):297781.
2. Malczyk Ź, Oświęcimska JM. Gastrointestinal complications and refeeding guidelines in patients with anorexia nervosa. *Psychiatr Pol* 30 avr. 2017;51(2):21929.
3. Kerem NC, Riskin A, Averin E, Srugo I, Kugelman A. Respiratory acidosis in adolescents with anorexia nervosa hospitalized for medical stabilization: a retrospective study. *Int J Eat Disord janv.* 2012;45(1):12530.
4. Casiero D, Frishman WH. Cardiovascular complications of eating disorders. *Cardiol Rev sept.* 2006;14(5):22731.
5. Neumärker KJ. Mortality and sudden death in anorexia nervosa. *Int J Eat Disord avr.* 1997;21(3):20512.
6. Tonhajzerova I, Mestanikova A, Jurko A Jr, Grendar M, Langer P, Ondrejka I, et al. Arterial stiffness and haemodynamic regulation in adolescent anorexia nervosa versus obesity. *Appl Physiol Nutr Metab janv.* 2020;45(1):8190.
7. Abdelhadi Z, Bladbjerg EM, Jensen DM, Schousboe A, Støving RK. Venous thromboembolism in anorexia nervosa: four cases from a specialized unit. Indication for thromboprophylaxis? *Eat Weight Disord [En ligne].* 17 déc 2019; Disponible: <http://dx.doi.org/10.1007/s40519-019-00830-5>.
8. Jensen M, Thomalla G. Causes and Secondary Prevention of Acute Ischemic Stroke in Adults. *Hamostaseologie févr.* 2020;40(1):2230.
9. Putaala Jukka, Metso Antti J, Metso Tiina M, Nina K, Yvonn K, Elena H, et al. Analysis of 1008 Consecutive Patients Aged 15 to 49 With First-Ever Ischemic Stroke. *Stroke. American Heart Association;* 1 avr 2009;40(4):1195203.
10. Nadav L, Gur AY, Korczyn AD, Bornstein NM. Stroke in hospitalized patients: are there special risk factors? *Cerebrovasc Dis.* 2002;13(2):12731.
11. Kikura M, Bateman BT, Tanaka KA. Perioperative ischemic stroke in non-cardiovascular surgery patients. *J Anesth oct.* 2010;24(5):7338.
12. Bahouth MN, Gottesman RF, Szanton SL. Primary « dehydration » and acute stroke: a systematic research review. *J Neurol oct.* 2018;265(10):216781.
13. Kashani K, Rosner MH, Ostermann M. Creatinine: From physiology to clinical application. *Eur J Intern Med févr.* 2020;72:914.
14. Stella AB, Gaio M, Furlanis G, Ridolfi M, Ajčević M, Sartori A, et al. Prevalence of hypohydration and its association with stroke severity and independence outcomes in acute ischemic stroke patients. *J*

Clin Neurosci. Elsevier Ltd; 72:2816.

15. Lin CJ, Yang JT, Huang YC, Tsai YH, Lee MH, Lee M, et al. Favorable outcome of blood urea nitrogen/creatinine-based hydration therapy 3 months after acute ischemic stroke. *Am J Emerg Med* déc. 2016;34(12):24148.
16. Zhuang P, Wo D, Xu Z-G, Wei W, Mao H-M. Dynamic changes in plasma tissue plasminogen activator, plasminogen activator inhibitor-1 and beta-thromboglobulin content in ischemic stroke. *J Clin Neurosci* juill. 2015;22(7):11237.
17. Kataoka S, Hirose G, Hori A, Shirakawa T, Saigan T. Activation of thrombosis and fibrinolysis following brain infarction. *Journal of the Neurological Sciences*. 29 août 2000;(181):828.
18. Yokote A, Hashimoto K, Bikei R, Nakamoto H. Elevated Release of Beta-thromboglobulin and Platelet Factor 4 in Cerebral Infarction Patients with Branch Atheromatous Disease: A Preliminary Report. *Neurol Med Chir*. sept 2015;15(10):80912. 55(.
19. Oświęcimaska J, Malczyk Ż, Szymłak A, Mikołajczak A, Ziara K, Zamlynski J, et al. Changes in Platelet Count and Size Indices in Adolescent Patients With Anorexia Nervosa. *Clin Appl Thromb Hemost* sept. 2017;23(6):5626.
20. Alvitigala BY, Azra MAF, Kottahachchi DU, Jayasekera MMPT, Wijesinghe RANK. A study of association between platelet volume indices and ST elevation myocardial infarction. *Int J Cardiol Heart Vasc* déc. 2018;21:710.
21. Lang F, Ritz E, Voelkl J, Alesutan I. Vascular calcification–is aldosterone a culprit? *Nephrol Dial Transplant* mai. 2013;28(5):10804.
22. Arnaoutis G, Kavouras SA, Stratakis N, Likka M, Mitrakou A, Papamichael C, et al. The effect of hypohydration on endothelial function in young healthy adults. *Eur J Nutr* avr. 2017;56(3):12117.

Figures

Patient 1



Patient 2

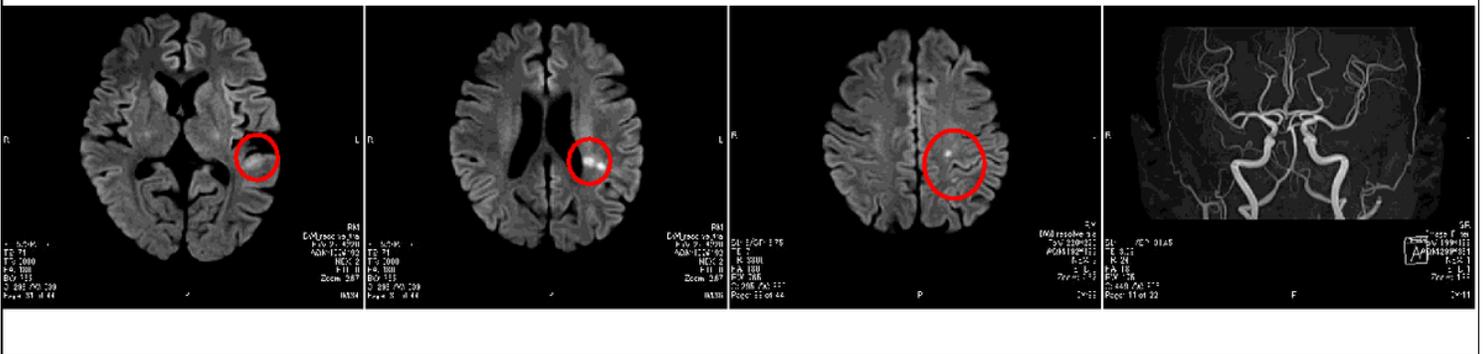
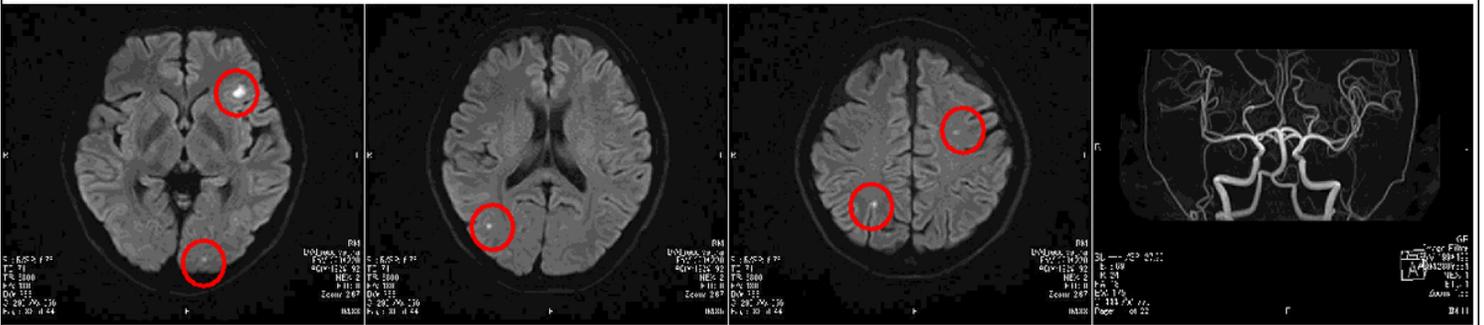


Figure 1

Brain MRI (Patient 1, 2). Patient 1 (Upper row) Brain MRI revealed disseminated cortical infarctions bilaterally. MR angiography showed no arterial stenosis. Patient 2 (Lower row) Brain MRI revealed focal brain infarction in the white matter underlying the left temporal transverse temporal gyrus, the left supramarginal gyrus, and the left parietal cortex. MR angiography showed no arterial stenosis.

Patient 1



Patient 2

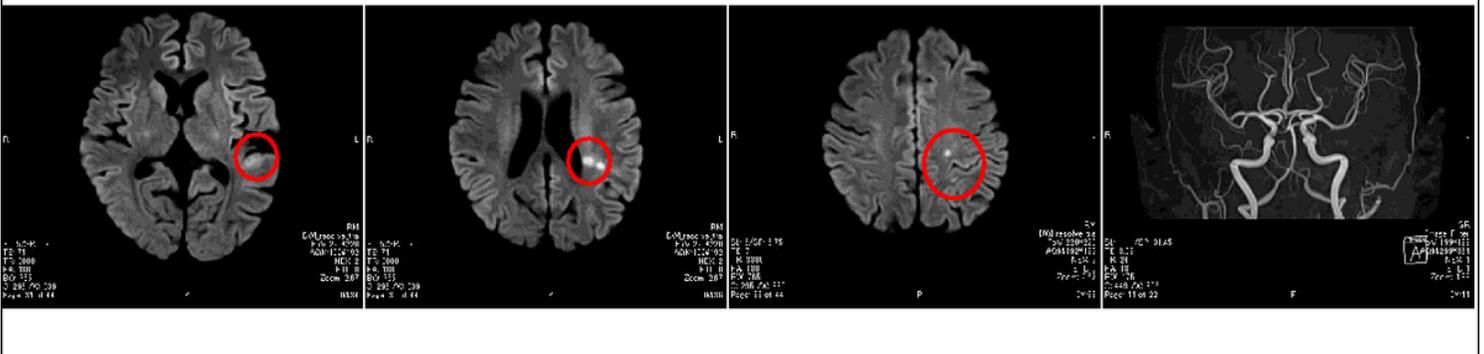


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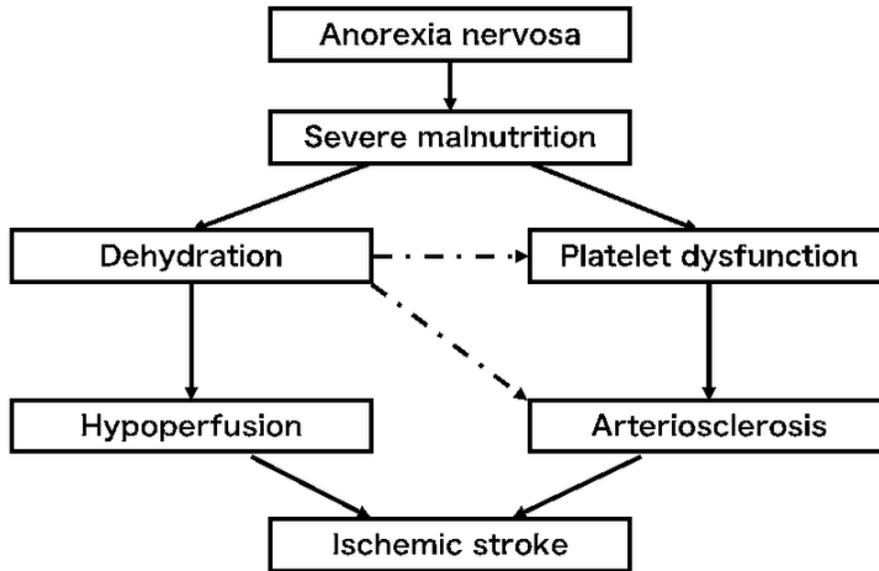


Figure 2

Relationships among hypoperfusion, arteriosclerosis, and malnutrition due to anorexia nervosa. The relationships among dehydration, arteriosclerosis, and severe malnutrition are quite complex. Severe malnutrition in association with severe AN may induce hypoperfusion due to dehydration and arteriosclerosis in association with platelet dysfunction. Moreover, hypovolemia caused by dehydration can induce arteriosclerosis and dehydration itself may be associated with impaired endothelial function.

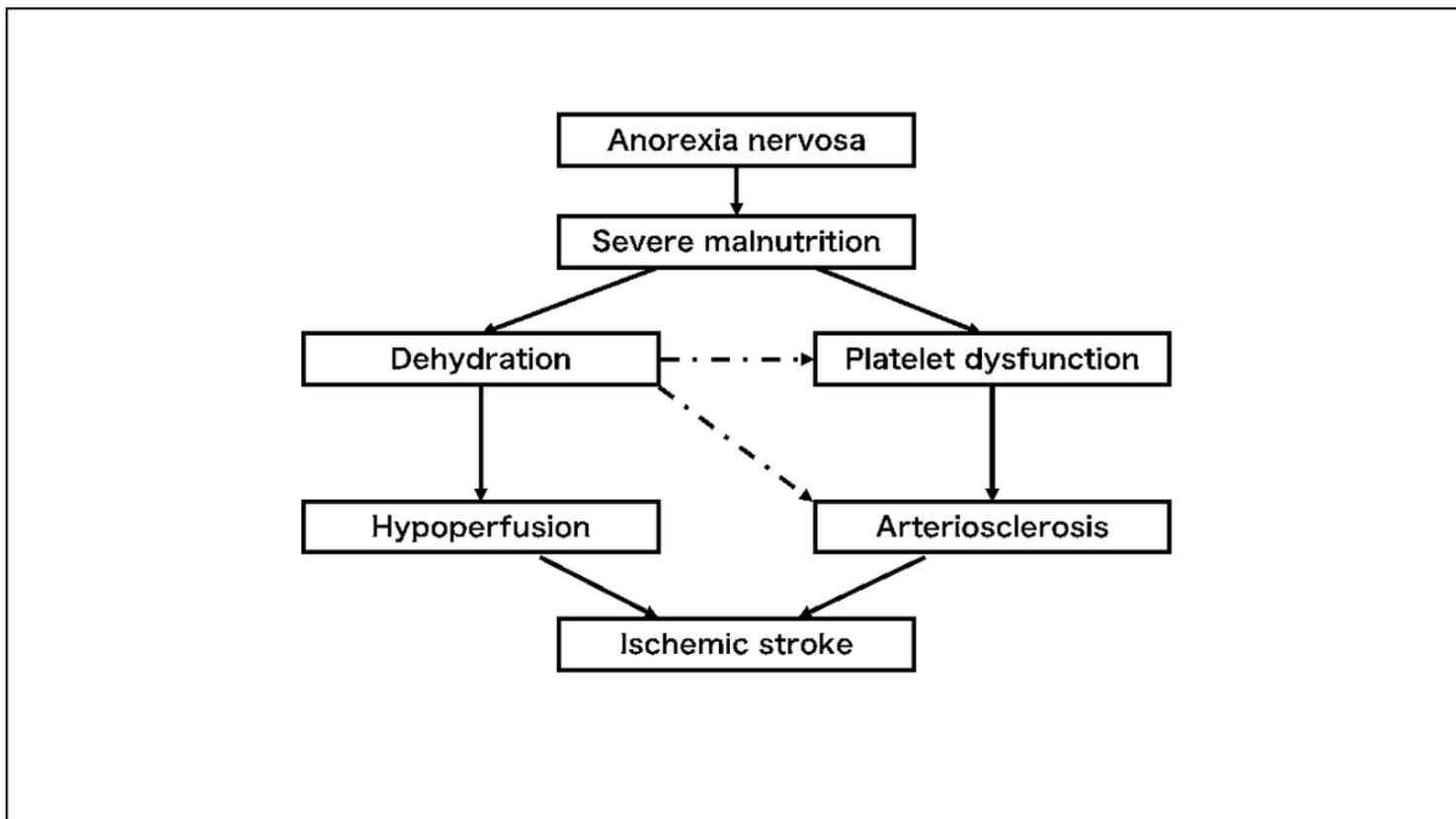


Figure 2

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