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Literature reviews of stroke with hypereosinophilic syndrome

Ryohei Ono *, Togo Iwahana, Hirotoshi Kato, Sho Okada, Yoshio Kobayashi

Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan

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ABSTRACT

Hypereosinophilic syndrome (HES) is defined by persistently elevated blood eosinophil levels and is associated with evidence of organ damage. Cardiovascular involvement in HES is most commonly associated with Loffler endocarditis (cardiac HES). Cardiac HES is typically characterized by progressive subendocardial fibrosis with overlying mural thrombus formation, leading to restrictive dysfunction of the left ventricle. The thrombus from cardiac HES could result in cardiogenic stroke; however, most of the stroke cases with HES were not associated with huge thromboembolism rather multiple infarcts in the watershed area. The major clinical features of 97 previously reported cases of stroke with HES are as follows: the median age was 52 years, of which 61 (63%) were men; the initial presenting symptoms were neurological (73%), followed by headache (16%), respiratory symptoms (9%), and visual symptoms (9%). Almost half of the cases were diagnosed with cardiac HES. The characteristics of cardiac findings were mural thrombi, endomyocardial fibrosis, and a restrictive pattern of heart failure. Cerebral findings revealed 78 cases (80%) were described as multiple infarctions and 55 cases (57 %) were involved with watershed areas, whereas 11 cases (11 %) were described as embolic stroke for one proximal large-vessel occlusion. Regarding treatment, 71 (73%), 28 (29%), and 16 (16%) patients were treated with steroids, anticoagulants, and antiplatelets, respectively. The overall mortality and recovery rates were 11% and 89%, respectively. Physicians should know most cases of stroke with HES are characterized by multiple infarctions in the watershed area, and cardiac HES is not always associated with stroke.

1. Introduction

Hypereosinophilic syndrome (HES) is a rare blood disorder in which eosinophils invade blood vessels, causing multi-organ failure. HES is defined by persistently elevated blood eosinophil levels (>1500/μL) and is associated with evidence of organ damage [1].

HES can present with neurological manifestations, including stroke, encephalopathy, and sensory polyneuropathy. The cause of cerebral infarction is thought to be thromboembolism or cerebrovascular endothelial toxicity of eosinophils. A thromboembolism may affect the vascular border zone, which is usually related to infarction due to prolonged systemic hypotension or proximal carotid arterial obstruction [2]. Cerebral infarction has also been associated with thromboembolic events originating from an intraventricular thrombus; however, the pathogenesis of eosinophilia-associated stroke, as one of the most severe complications of HES, remains poorly understood.

Cardiovascular involvement in HES is most commonly associated with Loffler endocarditis (cardiac HES), which was first reported by Loffler in 1936 [3]. Cardiac HES is characterized by progressive subendocardial fibrosis with overlying mural thrombus formation, leading to restrictive dysfunction of the left ventricle [4]. This fibrosis or thrombus from cardiac HES could result in cardiogenic stroke; however, most of the cases of stroke with HES were not associated with huge thromboembolism rather multiple infarcts in the watershed area. The proposed pathophysiological mechanisms include microembolism? from endomyocardial fibrosis or local thromboses due to eosinophil-induced endothelial dysfunction of the cerebral vessels [5]. However, the relationship between stroke and cardiac HES remains unknown.

We searched PubMed to identify case reports of stroke with HES and found 97 cases that have been reported from January 2000 to October 2021 [2,4,6–80]. Herein, previously reported cases of stroke with HES were reviewed and summarized.

2. Methods

This literature review has been reported in concordance with guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA) [81]. Approval from

* Corresponding author.
E-mail address: ryohei_ono_0820@yahoo.co.jp (R. Ono).

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the institutional review board was not required since the data was publicly available.

2.1. Literature search strategy and data sources

We systematically reviewed the literature for reports of characteristics and clinical outcomes of patients with stroke with HES. We searched PubMed for all articles published from January 2000 to October 2021 using the following keywords or MeSH terms: ((“eosinophil s”[All Fields] OR “eosinophile”[All Fields] OR “eosinophiles”[All Fields] OR “eosinophilic”[All Fields] OR “eosinophillic”[All Fields] OR “eosinophills”[All Fields] OR “eosinophils”[MeSH Terms] OR “eosinophils”[All Fields] OR “eosinophil”[All Fields]) AND (“stroke”[MeSH Terms] OR “stroke”[All Fields] OR “strokes”[All Fields] OR “stroke s”[All Fields])) OR ((“stroke”[MeSH Terms] OR “stroke”[All Fields] OR “strokes”[All Fields] OR “stroke s”[All Fields] OR (“watershed”[All Fields] OR “watershed s”[All Fields] OR “watersheds”[All Fields]) OR (“central nervous system”[MeSH Terms] OR (“central”[All Fields] AND “nervous”[All Fields] AND “system”[All Fields]) OR “central nervous system”[All Fields]) OR (“neurologic manifestations”[MeSH Terms] OR (“neurologic”[All Fields] AND “manifestations”[All Fields]) OR “neurologic manifestations”[All Fields] OR “neurologic”[All Fields] OR “neurological”[All Fields] OR “neurologically”[All Fields])) AND (“hypereosinophilic syndrome”[MeSH Terms] OR (“hypereosinophilic”[All Fields] AND “syndrome”[All Fields]) OR “hypereosinophilic syndrome”[All Fields])).

2.2. Case selection

All articles retrieved from the systematic search were exported to EndNote Reference Manager (Version X9; Clarivate Analytics, Philadelphia, Pennsylvania). The articles were then assessed at title and abstract level, after which full text were read to confirm relevance. The following pre-defined inclusion criteria was used: (1) human case reports written in English, (2) cases with elevated blood eosinophil levels (>1500/μL) and stroke, and (3) reports with available clinical,

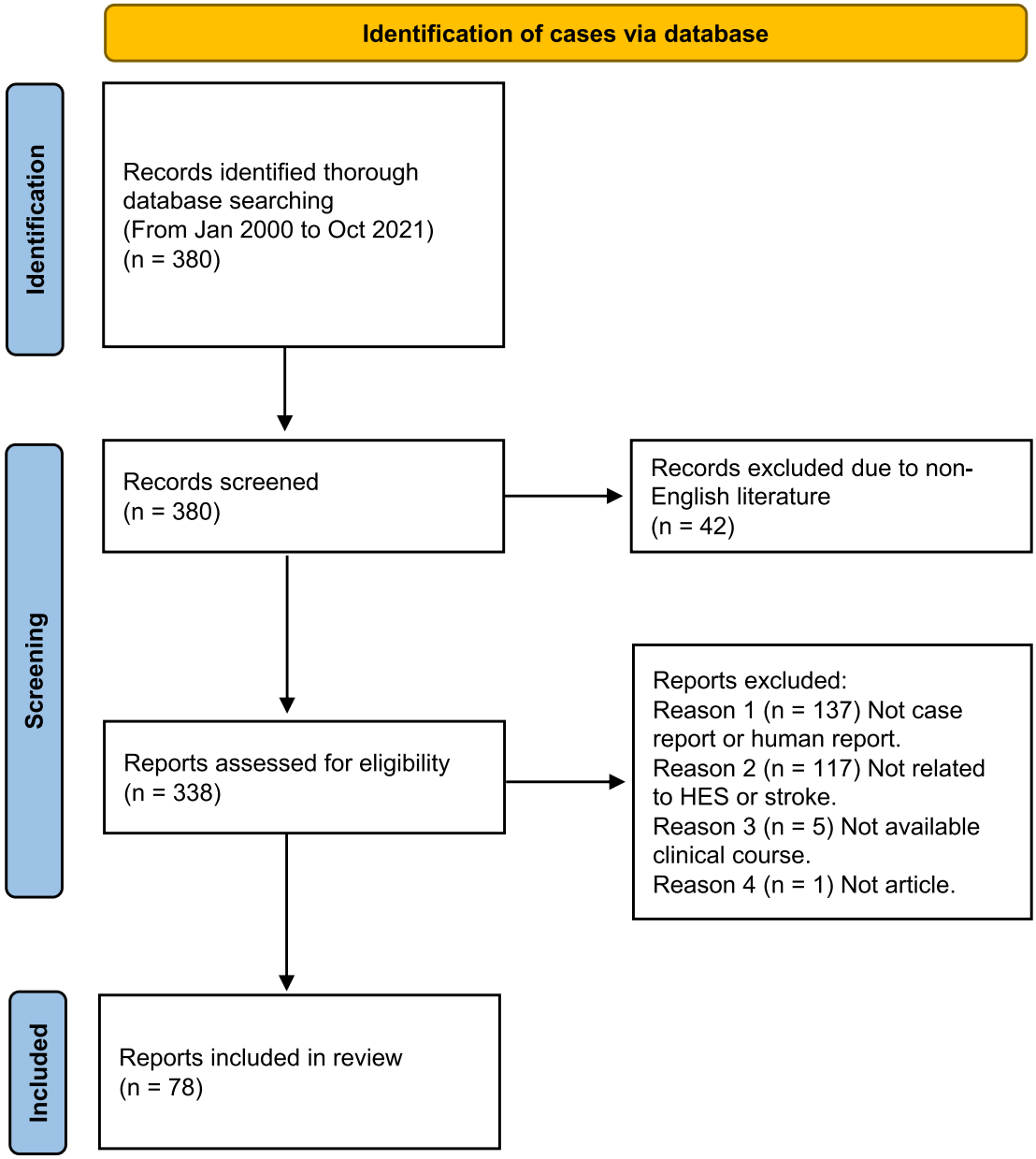

Fig. 1. PRISMA flowchart outlining literature search.

biological and radiological data and outcomes.

3. Results

3.1. Literature search

The initial literature search yielded 380 potentially relevant articles. After applying the predetermined eligibility criteria, 78 reports (97 cases) were selected for inclusion in this literature review. The PRISMA flowchart summarizes the results of our literature search (Fig. 1).

3.2. Literature review

The major clinical features including cardiac and cerebral findings of the 97 previously reported cases of stroke with HES are summarized in Table 1[2,4,6–80].

The median age of the population was 52 years (interquartile range, 37–63 years of age), of which 61 (63%) were male and 35 were female. Eight (8%) of the identified cases were patients younger than 20 years of age. The initial presenting symptoms of stroke with HES were neurological symptoms including weakness, dysarthria, and confusion (n = 71, 73%), followed by headache (n = 16, 16%), respiratory symptoms (n = 9, 9%), visual symptoms such as diplopia (n = 9, 9%), fever (n = 7, 7%), chest or back pain (n = 4, 4%), and skin symptoms (n = 4, 4%). Throughout the process, concurrent neurological and respiratory events were noted in only two cases (2%). The median total eosinophil counts was 8.1 × 10^3/μL (interquartile range, 4.1–13.8 × 10^3/μL).

In this category, idiopathic HES was the most common (n = 62, 64%), followed by secondary HES (n = 26, 27%) and primary HES (n = 8, 8%). One case was unclassified because the patient was considered to have eosinophilic granulomatosis with polyangiitis (EGPA) or idiopathic HES. In the cases of secondary HES, EGPA was the most popular cause (11 cases). Lymphocytic variant HES was reported in four cases, although it is a rare entity. In addition, three cases parasitic infection were reported, while there were two cases of systemic lupus erythematosus.

Cardiac investigations were performed in 82 cases (85%); however, atrial fibrillation was detected in only 2 cases. Major cardiac investigations included transthoracic echocardiography (n = 76, 78%), electrocardiogram (n = 33, 34%), magnetic resonance imaging (n = 19, 20%), transesophageal echocardiography (n = 16, 16%), and Holter electrocardiogram (n = 10, 10%). As for cardiac findings, 36 cases (45%) were diagnosed with cardiac HES, while 44 cases (55%) were not. Thus, cardiac HES was not always associated with stroke, which suggested that the stroke was caused by not only cardiac embolism but also other mechanisms including hyperviscosity and hypercoagulability of eosinophilia. Therefore, screening for cardiac HES is essential in patients with stroke with HES, but stroke may still occur even if no cardiac findings are found. The characteristics of cardiac findings in patients with HES and stroke were mural thrombi, endomyocardial fibrosis, and a restrictive pattern of heart failure.

Cerebral findings revealed that 78 cases (80%) were described as multiple infarctions and 55 cases (57%) were involved with watershed areas, whereas 11 cases (11%) were described as embolic stroke for one proximal large-vessel occlusion. Based on these results, stroke with HES is characterized by multiple watershed infarctions. For the treatments, 71 patients (73%) used steroids and 11 patients (11%) used imatinib. A total of 28 patients (29%) were treated with anticoagulant agents, while 16 patients (16%) received antiplatelet therapy. Some patients only used steroids without anti(?)coagulation therapy, but obtained favorable outcomes. This suggests that control of eosinophilia is also essential for the secondary prevention of stroke. Surgical treatment was performed in two patients; one was surgical removal of EMF for heart failure and the other one was surgical decompression for brain herniation. Relapse of stroke occurred in six cases. Of note, elevation of eosinophilia (range, 2256–32,000/μL) was observed at relapse in all these cases. Three cases with the relapse of stroke were initially using only antiplatelet therapy; however, elevation of eosinophilia remained, and stroke occurred again. The overall mortality rate was 11%, and the recovery rate was 89% (alive: 72 patients, dead: nine patients, while outcome for 16 patients were not described). The detailed causes of death were brain infarction including brain herniation (n = 3), cardiac failure (n = 3), acute lymphoblastic leukemia (n = 1), renal cell carcinoma (n = 1), and an unknown cause (n = 1).

4. Discussion

HES is classified into three groups: (A) idiopathic HES, in which no underlying disease or syndrome is apparent; (B) primary (clonal/neoplastic), which includes acute leukemia, chronic myeloid disorders, and myeloproliferative syndromes; (C) secondary (reactive), which is caused by infections, allergic disorders, medications, autoimmune disorders, endocrinopathies, and metastatic malignancies [82]. FIP1-like-1-platelet-derived growth factor receptor-alpha (FIP1L1-PDGFRA) results in a constitutively active tyrosine kinase which induces uncontrolled cell proliferation and primary HES, and FIP1L1-PDGFRA positive myeloid neoplasm with eosinophilia is reported to be accounting for up to 10% of all patients with HES [83]. In fact, five cases of FIP1L1-PDGFRA positive HES with stroke (5%) were reported in our review. Previous review reported 9.3% of FIP1L1-PDGFRA positive HES had at least one ischemic stroke [83]. Among secondary (reactive HES), lymphocytic variant HES is defined by the presence of a Th2 T-cell subset overproducing interleukin-5 (IL-5). These clones are described to overproduce eosinophil-promoting cytokines such as IL-5, causing a reactive eosinophilia [42]. In the cases of secondary HES, EGPA was the most popular cause in our review. Previous review in a large series of central nervous system involvement in EGPA reported 52% of patients had cerebral infarction on radiological assessment [84]. Complete evaluation of systemic involvement of idiopathic HES is mandatory, and early intervention may prevent the deterioration of this disease [74]. Eosinophils can accumulate in multiple organs, including the heart, skin, nervous system, and lungs, causing end-organ damage in patients with HES [46]. In the classical view of eosinophil-induced organ damage in HES, tissue infiltrates are often accompanied by tissue fibrosis, thrombosis, and/or the extracellular deposition of eosinophil-derived proteins [85]. The involvement of the heart can lead to an intraventricular thrombus because of the infiltration of eosinophils into the endomyocardium. Thrombi formation may also occur on damaged endocardium and valve leaflets. Cardiac lesions such as eosinophilic myocarditis or Loffler's fibroblastic endocarditis are thought to occur due to the toxicity of the eosinophilic basic protein released by eosinophilic granulocytes, causing local destruction of the endocardium with subjacent fibrosis of the myocardium, leading to the formation of intracardiac thrombi [46]. These proteins play an important role in platelet activation and thrombus formation by inhibiting thrombomodulin. Activated eosinophils and eosinophil granule proteins were detected within the necrotic and thrombotic lesions and were found mainly in acute tissue damage in the endocardium and in the walls of small blood vessels. These findings indicate a potential role of eosinophils in vascular injury and inflammation [86]. Other clinical features of eosinophil-driven cardiovascular toxicity include endomyocardial fibrosis, eosinophil vasculitis and venous thromboembolism [85,87,88]. Eosinophil-mediated endomyocardial damage leads subendocardial eosinophilic infiltrates at the early, and generally asymptomatic stage. As disease progresses, patients typically develop intracardiac mural thrombi and may experience variable degrees of heart failure due to valve damage and/or endocardial fibrosis [87]. As for vasculitis, EGPA had been considered as the diagnosis in the context of eosinophilia. Although EGPA is classified as an antineutrophil-cytoplasmic-antibody (ANCA)-associated vasculitis, only 30% of affected patients have ANCAs; thus, differentiating between HES and ANCA-negative EGPA is difficult. Recent studies revealed several ANCA- negative, asthma-free patients with HES are classified as

Table 1
Literature review of stroke with hypereosinophilic syndrome.

Case	Author	Year [Reference]	Age	Sex	Initial presentation	Eosinophil (/μL)	Cause of hypereosinophlia	Cardiac investigation	Presence of AF	Cardiac findings	Cardiac HES	Cerebral findings	Treatment	Relapse of stroke after treatment	Outcome
1	Kwon	2001 [6]	65	M	Seizures, left hemiparesis	3,210	Idiopathic HES	ECG, TTE, Thallium–201 myocardial scan	No	Mild to moderate global hypokinesia, perfusion defect in the posterior wall	No	Multiple, watershed area	PSL	No	Alive at 4 years
2	Kwon	2001 [6]	42	M	Chest discomfort, weakness in the right hand	10,510	Idiopathic HES	TTE	ND	LV wall thickness with layering of endocardial echogenic deposits obliterating the ventricular apex	Yes	Multiple, watershed area	PSL	No	Alive at 2 months
3	Kwon	2001 [6]	60	M	Gait disturbance, headache, confusion	6,550	Idiopathic HES	ECG, TTE	No	Unremarkable	No	Multiple, watershed area	PSL	No	Alive at 2 years
4	Engelmann	2004[7]	40	M	Cough, shoulder pain, facial paresis, sensomotor hemiparesis, dysarthria	16,992	Idiopathic HES	ECG, TTE, coronary angiography	No	Floating structure, endomyocardial thickening	Yes	Multiple, watershed area	PSL, heparin	ND	Alive at 6 months
5	Frickhofen	2004 [8]	33	M	Headache, weakness of the right arm	2,300	Primary HES (Chronic eosinophilic leukemias)	ND	ND	ND	No	Multiple foci of the left parietal cortex and the cerebellum	Imatinib	No	Alive at 16 months
6	Sarazin	2004[9]	51	M	Confusion, left hemiplegia	26,000 (Initial) 32,000 (Relapse)	Idiopathic HES	TEE, cardiac MRI	ND	EMF, mural thrombi	Yes	Multiple, watershed area	PSL, etoposide, anticoagulant, aspirin	Yes (2 years later)	Died at 2 years
7	Sarazin	2004[9]	25	F	Headache, gait and limb ataxia, personality changes, loss of memory and attention, apathy, and lethargy	3,900	Secondary HES (S mansoni infection)	ECG, TTE, cardiac CT	No	Non-calcified EMF	Yes	Multiple, watershed area	Praziquantel, Aspirin, surgical removal of EMF	No	Alive at 16 months
8	Kanno	2005 [10]	34	F	Subcutaneous induration	11,280	EGPA or idiopathic HES	Autopsy	ND	Endocarditis, mural thrombi	Yes	Hemorrhagic infarction of left cerebral hemisphere, brain herniation	PSL, surgical decompression of brain	ND	Died at 33 days
9	Tsuda	2005 [11]	30	M	Horizontal diplopia	21,054	Secondary HES (EGPA)	ND	ND	ND	No	The left superior median mesencephalic branch of the posterior cerebral artery	PSL	No	ND
10	Cecchi	2006 [12]	65	F	Right hemiplegia, aphasia, headach	1,500	Secondary HES (eosinophilic fascilitis)	ND	ND	ND	No	Left frontal hematoma, multiple vascular narrowings of anterior and middle cerebral arteries	Dexamethasone	No	Alive at 1 year
11	Garg	2006 [13]	33	M	Hemiplegia	13,000	Idiopathic HES	ND	ND	ND	No	Infarct in right temporoparietal	PSL, heparin, hydroxyurea, imatinib	ND	Alive at 3 months

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Table 1 (*continued*)

Case	Author	Year [Reference]	Age	Sex	Initial presentation	Eosinophil (/μL)	Cause of hypereosinophlia	Cardiac investigation	Presence of AF	Cardiac findings	Cardiac HES	Cerebral findings	Treatment	Relapse of stroke after treatment	Outcome
												region (M1 embolization)			
12	Sakuta	2006 [14]	7	M	Headache, vomiting	15,200	Idiopathic HES	ECG, TTE	No	Unremarkable	No	Sagittal sinus thrombosis and right cerebral hemorrhage	Heparin, warfarin	No	Alive at 15 months
13	Barge	2008 [15]	48	M	Left facial nerve palsy with reduced strength in the left hand	(6.6 g/dL)	Secondary HES (Kimura's disease)	TTE	ND	Vegetations	Yes	Right frontal ischemia	PSL, warfarin	ND	ND
14	Chang	2008 [16]	43	M	Unsteady gait, diplopia	1,134 (Initial) 2,256 (Relapse)	Idiopathic HES	ECG, TTE, TEE	No	Unremarkable	No	Left thalamus and centrum semiovale infarction	PSL, aspirin	Yes (3 weeks later)	Alive at 2 years
15	McMillan	2008 [17]	16	M	Cough, fever	55,300	Idiopathic HES	TTE	ND	Unremarkable	No	Multiple, watershed area	Methylprednisone, hydroxyurea	No	Alive at 9 months
16	Noureen	2008 [18]	6	F	Fever, weakness of the right limbs	27,468	Idiopathic HES	None	ND	ND	No	Infarction involving left internal capsule and basal ganglia	PSL, aspirin, hydroxyurea	No	Alive at 6 months
17	Chang	2009 [19]	35	F	Left-sided weakness	2,718	Idiopathic HES	ECG, TTE, cardiac CT, cardiac MRI	No	Apical thrombus, EMF	Yes	Multiple embolic cerebral infarctions	PSL, anticoagulant	No	Alive at 1 month
18	Fazel	2009 [20]	64	M	Blurred vision, diplopia, headache	6,077	Idiopathic HES	ECG, TTE, cardiac MRI	No	Mobile thrombus, delayed hyperenhancement of the inferior wall	Yes	Multiple, watershed area	PSL, aspirin	No	Alive at 10 months
19	Grigoryan	2009 [21]	48	M	Weight loss, paresthesias	4,100	Idiopathic HES	ECG, TEE	No	Mild LV dysfunction without mural thrombus or vegetations	Yes	Multiple, watershed area	Methylprednisolone	No	Died at 22 days
20	Kono	2009 [22]	79	M	Right hemiparesis, left-sided visual field defect	23,175	Idiopathic HES	TTE, TEE	No	Unremarkable	No	Multiple, watershed area	PSL, aspirin	No	Alive at 2 months
21	Lin	2009 [23]	67	F	Confusion, weakness of the right limbs	1,970	Idiopathic HES	Holter ECG, TTE, cardiac MRI	No	Thickening of the LV endocardium, reduction of LV cavity, immobile thrombus	Yes	Multiple, watershed area, the absence of left internal carotid artery and middle cerebral artery	Hydrocortisone, PSL, anticoagulants	No	Alive at 9 months
22	Perini	2009 [24]	63	F	Sustained eosinophilia	40,000 (Initial) 6,480 (Relapse)	Idiopathic HES	TTE, TEE	No	No intracardiac thrombus, presence of patent foramen ovale	No	Multiple, watershed area	PSL, imatinib, anticoagulants, hydroxyurea, interferon alfa	Yes (1 week later)	Alive
23	Lee	2009 [2]	52	M	General weakness	5,500	Idiopathic HES	TTE	ND	Mild LV inferior wall hypokinesia	No	Multiple, watershed area, focal intracerebral hemorrhage	PSL, aspirin	No	Alive at 2 weeks
24	Ahn	2010 [25]	56	M	Bilateral weakness, speech disturbance and swallowing difficulty	3,190	Idiopathic HES	Holter ECG, TTE, TEE	No	Unremarkable	No	Multiple, watershed area	PSL, antiplatelet	No	ND

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Table 1 (*continued*)

Case	Author	Year [Reference]	Age	Sex	Initial presentation	Eosinophil (/μL)	Cause of hypereosinophlia	Cardiac investigation	Presence of AF	Cardiac findings	Cardiac HES	Cerebral findings	Treatment	Relapse of stroke after treatment	Outcome
25	Aydogdu	2010 [26]	15	M	Confusion, quadriparesis and ataxia	6,456	Secondary HES (SLE)	TTE	ND	LV myocardial thicking, mobile thrombus	Yes	Multiple areas of infarction	Metilprednisolone, warfarin, chloroquine	No	Alive at 6 weeks
26	Sethi	2010 [27]	52	M	Right-sided weakness and slurring of speech	7,534	Idiopathic HES	TTE	ND	Unremarkable	No	Multiple, watershed area	Aspirin	ND	Alive at 2 months
27	Sethi	2010 [27]	47	M	Right flank and leg pain	18,900	Idiopathic HES	TTE	ND	Mild LV dysfunction without mural thrombus	No	Multiple, watershed area	Steroid	No	Alive at 1 year
28	Sethi	2010 [27]	46	F	Chest pain	67,890	Idiopathic HES	ECG, TTE	No	Inferior wall myocardial infarction	No	Multiple, watershed area, embolic cerebral infarctions	Steroid, imatinib	No	Alive at 7 months
29	Takeuchi	2010 [28]	23	F	Aphasia, right-sided hemiparesis	1,68,000	Idiopathic HES	ECG, TTE	No	Unremarkable	No	Occlusion of the M1 segment of the left middle cerebral artery	Transarterial thrombolysis (pro-urokinase)	No	Alive at 60 days
30	D'Orazio	2011 [29]	15	M	Chest pain, dyspnea	8,471	Idiopathic HES	ECG, cardiac catheterization	ND	Subendocardial infarction	No	Multiple, watershed area	PSL, imatinib	No	Alive at 5 months
31	Dujardin	2011 [5]	56	M	Headache, clumsiness of his right hand, numbness in the right side of his face	3,500	Secondary HES (T-cell-mediated HES)	ECG, holter ECG, TTE, TEE, cardiac CT, cardiac MRI	No	Unremarkable	No	Multiple, watershed area	Acetylsalicylic acid, methylprednisolone	No	Alive at 6 months
32	Hus	2011 [30]	28	M	Headache, confusion, weakness of his right arm	15,000	Primary HES (FIP1L1/PDGFRA-associated HES)	TTE	ND	Unremarkable	No	Multiple, watershed area	Methylprednisolone, PSL, imatinib	No	Alive at 6 months
33	van Gaalen	2011 [31]	18	F	Numbness on the left side of her body and face	3,870	Secondary HES (T-lymphocytic variants HES)	ECG, TTE	No	Unremarkable	No	Dissecting aneurysm of the right posterior inferior cerebellar artery	PSL, interferon α, aspirin, dipyridamol	No	Alive
35	Cheng	2012 [32]	60	M	Right hemiparesis	13,676	Secondary HES (Churg–Strauss Syndrome)	ECG, holter ECG, TTE, coronary angiography	No	EMF	Yes	Multiple, watershed area, cortically and subcortically	PSL, cyclophosphamide, warfarin	No	Alive at 4 months
34	Hwang	2012 [33]	69	M	Headache, generalized weakness	3,356	Secondary HES (Clonorchis sinensis infestation)	ECG, TTE, TEE	No	Mild diastolic dysfunction without mural thrombus or vegetations	Yes	Multiple, watershed area	Praziquantel	No	Alive at 1 month
36	Sharma	2012 [34]	11	M	Right sided hemiparesis	3,792	Idiopathic HES	TTE	ND	Mildly dilated left ventricle, with 60% ejection fraction and multiple friable clots	No	Left lenticular nucleus infarct	Heparin, warfarin, hydroxyurea	No	Alive at 3 months
37	Tanaka	2012 [35]	77	F	Gait disturbance	4,480	Secondary HES (EGPA)	ND	Yes	ND	ND	Infarction in the right cerebellum	PSL	No	Alive
38	Todenhöfer	2012 [36]	46	M	Fever, reduced general condition	12,654	Primary HES (Paraneoplastic hypereosinophilia)	ECG, TTE	No	LV dysfunction with inferior hypokinesia,	No	Multiple, watershed area	PSL, hydroxiurea, vincristine, cytarabine	No	Died after 4 months

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Table 1 (*continued*)

Case	Author	Year [Reference]	Age	Sex	Initial presentation	Eosinophil (/μL)	Cause of hypereosinophlia	Cardiac investigation	Presence of AF	Cardiac findings	Cardiac HES	Cerebral findings	Treatment	Relapse of stroke after treatment	Outcome
										mild MR without endocarditis					
39	Aida	2013 [37]	33	F	Back pain	10,400	Primary HES (Acute lymphoblastic leukemia)	TTE	ND	ND	No	Multiple, watershed area	Hydroxiurea, warfarin	No	Died at 3 months
40	Aida	2013 [37]	41	M	Disarthria, left hemiparesia	2,550 (Initial) 3,610 (Relapse)	Idiopathic HES	TTE, TEE, cardiac MRI	No	EMF	Yes	Multiple, watershed area	PSL, hidroxyurea	Yes (1 month later)	Alive at 6 years
41	Aida	2013 [37]	65	M	Memory loss	3,800	Idiopathic HES	TTE, TEE, cardiac MRI	No	EMF	Yes	Multiple, watershed area	PSL	No	Alive at 6 years
42	Aida	2013 [37]	64	F	Respiratory symptoms, weakness and loss of sensation in both legs	4,392	Idiopathic HES	TTE, cardiac MRI	No	LV thrombi, EMF	Yes	Multiple, watershed area	PSL, anticoagulant	No	Died at 3 months
43	Khwaja	2013 [38]	68	M	Neurological deficit	42,500	Idiopathic HES	ECG, TTE	No	Moderate MR with apical thrombi in both ventricles	Yes	Multiple embolic infarcts	Steroids, albendazole, anticoagulant	No	Died at 2 weeks
44	Wise	2013 [39]	66	M	Shortness of breath	5,100	Idiopathic HES	TTE	ND	Unremarkable	No	Shower of recent embolic infarcts	Corticosteroids, anticoagulants	No	Alive at 2 months
45	Yhim	2013 [40]	51	M	Dyspnea, chill	40,425	Idiopathic HES	TTE	ND	LV apical thickening with thrombi, restrictive mitral inflow	Yes	Multiple cerebral infarctions	Imatinib	No	Alive at 6 months
46	Lee	2014 [41]	37	M	Transient confusion, memory impairment	12,240	Idiopathic HES	TTE	ND	Unremarkable	ND	Occlusion of a branch of the right posterior cerebral artery	ND	ND	ND
47	Lee	2014 [41]	40	M	Confusion	2,800	Idiopathic HES	TTE	ND	Unremarkable	ND	ND	ND	ND	ND
48	Lee	2014 [41]	49	M	Confusion	28,300	Idiopathic HES	TTE	ND	Mild reginonal wall motion abnormality	ND	ND	Corticosteroid, hydroxyurea and interferon alpha	ND	ND
49	Lee	2014 [41]	49	M	Confusion, bilateral upper extremity weakness	5,200	Idiopathic HES	TTE	ND	Left ventricular hypertrophy	ND	Multiple, watershed area	ND	ND	ND
50	Lee	2014 [41]	58	F	Quadriparesis	1,650	Idiopathic HES	TTE	ND	Unremarkable	ND	Multiple, watershed area, hemorrhagic transformation in the parietal and occipital cortices	ND	ND	ND
51	Lee	2014 [41]	68	M	Hemiparesis	4,000	Idiopathic HES	TTE	ND	Unremarkable	ND	Multiple, watershed area	ND	ND	ND
52	Lee	2014 [41]	47	M	Hemiparesis	12,300	Idiopathic HES	TTE	ND	Unremarkable	ND	ND	ND	ND	ND
53	Lee	2014 [41]	43	M	Drowsy mental status, quadriparesis	5,015	Idiopathic HES	TTE	ND	Asymmetrical septal hypertrophy	ND	ND	ND	ND	ND
54	Lee	2014 [41]	49	M	Hemiparesis	6,360	Idiopathic HES	TTE	ND	Unremarkable	ND	ND	ND	ND	ND
55	Lee	2014 [41]	75	M	Dysarthria	3,130	Idiopathic HES	TTE	ND	Unremarkable	ND	Multiple, watershed area	ND	ND	ND

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Table 1 (*continued*)

Case	Author	Year [Reference]	Age	Sex	Initial presentation	Eosinophil (/μL)	Cause of hypereosinophlia	Cardiac investigation	Presence of AF	Cardiac findings	Cardiac HES	Cerebral findings	Treatment	Relapse of stroke after treatment	Outcome
56	Lefevre	2014 [42]	38	F	ND	3,000	Secondary HES (Lymphocytic variant HES)	ND	ND	Multiple coronary and supra-aortic vessels aneurysms	ND	Ischemic embolic stroke	PSL	No	Alive at 4.8 years
57	Lefevre	2014 [42]	36	M	Diplopia	4,900	Secondary HES (Lymphocytic variant HES)	ND	ND	ND	ND	Multiple, watershed area	PSL, methotrexate	No	Alive at 3.2 years
58	Taormina	2014 [43]	58	M	Right-sided hemiparesis and fever	7,400	Secondary HES (EGPA)	TTE, coronary angiography	ND	Unremarkable	No	Subarachnoid hemorrhage and infarction in left corona radiata and insula	PSL	No	Alive at 2 years
59	Wang	2014 [4]	56	M	Left hand numbness, headache	13,480	Idiopathic HES	TTE	ND	MR, TR, PH, endocardial thickening, thrombus	Yes	Multifocal infarctions, watershed area	PSL, warfarin	No	Alive at 10 days
60	Tong	2014 [44]	69	M	Limb weakness	5,520	Secondary HES (Ancylostom infection)	ECG, TTE, cardiac CT	No	Unremarkable	No	Multiple, watershed area	Antiparasite therapy	No	Alive at 1 month
61	Wu	2014 [45]	62	M	Hemiparesis	4,840	Idiopathic HES	ECG, TTE	No	Unremarkable	No	Multiple, watershed area	PSL, aspirin	No	Alive at 6 months
62	Bolz	2015 [46]	29	M	Hemihypesthesia, gait disturbance	27,860	Secondary HES (Heroin)	ECG, TTE, TEE, cardiac MRI	No	Unremarkable	No	Multiple, watershed area	PSL, methadone, aspirin	No	Alive at 2 weeks
63	Feske	2015 [47]	38	F	Headache, visual symptoms	3,234	Secondary HES (Parasitic infection)	ECG, TTE	No	Endocardial deposits	Yes	Multiple, watershed area	Ivermectin, albendazole, glucocorticoids, warfarin	No	Alive at 3 years
64	Lai	2015 [48]	52	M	Dyspnea, orthopnea	16,600	Idiopathic HES	TTE	ND	LV dysfunction, global increased LV wall thickness, thrombi	Yes	Multiple, watershed area	PSL, heparin	No	Died at 5 days
65	Rice	2015 [49]	39	M	Drowsiness, agitated confusion and headache	9,100	Idiopathic HES	TTE	ND	Unremarkable	No	Sparing of the white matter around the perivascular spaces	Methylprednisolone, cyclophosphamid, mycophenolate, PSL	No	Alive at 2 years
66	Zeng	2015 [50]	9	F	Malnutrition, fever, cough, diarrhea and polymorphous pruritic skin eruptions	28,980	Primary HES (FIP1L1/PDGFRA-associated HES)	TTE	ND	Mild LV dysfunction	No	Multiple softening focus within the right head	Corticosteroid, imatinib	No	Alive
67	Chalayer	2017 [51]	26	M	Headache, fever	20,000	Primary HES (PDGFRA-associated chronic eosinophilic leukemia)	TEE, cardiac MRI	No	EMF	Yes	Multiple cerebral emboli	Imatinib, corticosteroids	No	Alive at 6 months
68	Chen	2017 [52]	25	M	Headache, blurred vision	1,940 (Initial) 3,230 (Relapse)	Idiopathic HES	ND	ND	ND	ND	Right frontal and occipital lobe infarction	Antiplatelets, glucocorticoids	Yes (1 month later)	Alive at 6 months
69	Chen	2017 [52]	57	F	Numbness and weakness in her right upper extremity	7,160 (Initial) 3,940 (Relapse)	Idiopathic HES	ND	ND	ND	ND	Multiple cerebral infarcts	Antiplatelets, glucocorticoids	Yes (3 weeks later)	Alive at 5 months

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Table 1 (*continued*)

Case	Author	Year [Reference]	Age	Sex	Initial presentation	Eosinophil (/μL)	Cause of hypereosinophlia	Cardiac investigation	Presence of AF	Cardiac findings	Cardiac HES	Cerebral findings	Treatment	Relapse of stroke after treatment	Outcome
70	Lee	2017 [53]	30	M	Headache, aphasia	26,400	Primary HES (FIP1L1/PDGFRA-associated HES)	TTE	ND	Highly echogenic organized layer in the biventricular apex	Yes	Acute ischemic cerebral infarction in the left posterior middle cerebral artery	Imatinib, warfarin	No	Alive at 3 months
71	Mahovic	2017 [54]	61	M	Left-sided hemiparesis	11,000	Secondary HES (EGPA)	TTE, holter ECG	No	Unremarkable	No	Multiple, watershed area, stenosis of M1 and M2 segment of right middle cerebral artery (MCA) and M1 segment of left MCA	Methylprednisolone, cyclophosphamid	No	Alive at 3 months
72	Okada	2017 [55]	39	M	Left arm weakness and decrease in eyesight	12,814	Secondary HES (EGPA)	ECG, holter ECG, TEE	No	Mass lesion on the wall of the sinus of Valsalva	No	Multiple, watershed area	Warfarin	No	Alive at 3 months
73	Psychogios	2017 [56]	63	F	Right arm paresis	8,800	Secondary HES (EGPA)	TTE, TEE, cardiac MRI, coronary angiography	ND	Unremarkable	No	Multiple, watershed area	Anticoagulant	No	ND
74	Wang	2017 [57]	48	F	Acute change in mental status	3,200	Idiopathic HES	ECG, TEE, coronary angiography, cardiac MRI	No	Subendocardial edema, eosinophilic myocarditis	Yes	Multiple small acute infarcts in bilateral frontal, parietal, occipital, and temporal lobes	Ivermectin, PSL, anticoagulants	No	Alive at 3 months
75	Brunet	2018 [58]	70	M	Neck pain, bilateral upper extremity weakness, blurry vision	8,100	Idiopathic HES	TTE, cardiac MRI	No	Mild LV dysfunction, extensive patchy subendocardial delayed enhancement	Yes	Multiple, watershed area	PSL, mepolizumab	No	Alive
76	Mulroy	2018 [59]	27	F	Hemiparesis, aphasia	ND	Idiopathic HES	ND	ND	ND	No	Multiple, watershed area	ND	ND	ND
77	Chan	2019 [60]	64	F	Altered level of consciousness	6,300	Idiopathic HES	ECG, TTE, endomyocardial biopsy	No	Eosinophilic infiltration of the endomyocardium	Yes	Multiple, watershed area	Methylprednisolone, PSL	No	Alive at 1 month
78	Chiu	2019 [61]	63	F	Confusion	6,600	Idiopathic HES	TTE	No	Normal LV systolic function with a small basal inferior wall motion	Yes	Multiple, watershed area	PSL	No	Alive at 8 months
79	Kushwah	2019 [62]	60	F	Weakness of the left upper limb	13,800	Idiopathic HES	ECG, TTE	No	Unremarkable	No	Multiple, watershed area	PSL	No	Died after 3 months
80	Sakuta	2019 [63]	53	M	Consciousness disturbance, vomiting	17,000	Secondary HES (EGPA)	TTE, myocardial biopsy	ND	Multiple mobilized and tufted masses originating from theLV septum, preserved LV function, trivial MR	Yes	Multiple infarctions in the bilateral cerebrum and cerebellum with microbleeding	PSL	No	Alive at 1 year
81	Wasilewski	2019 [64]	56	F	Headache, encephalopathy	1,79,450	Idiopathic HES	ND	ND	Thrombus, leaflet restriction,MR, TR	Yes	Multiple, watershed area	ND	ND	ND

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Table 1 (*continued*)

Case	Author	Year [Reference]	Age	Sex	Initial presentation	Eosinophil (/μL)	Cause of hypereosinophlia	Cardiac investigation	Presence of AF	Cardiac findings	Cardiac HES	Cerebral findings	Treatment	Relapse of stroke after treatment	Outcome
82	Chua	2020 [65]	65	F	Hemiplegia, memory loss	12,000	Idiopathic HES	Holter ECG, TTE	No	Unremarkable	No	Multiple infarctions over the left thalamus, splenium of the corpus callosum, medial aspect of left temporal lobe and left occipital lobe	PSL	No	Alive at 3 months
83	Demetriades	2020 [66]	57	F	Headache, lethargy, confusion, reduced consciousness	13,000	Idiopathic HES	ECG, TTE, cardiac MRI	No	Apical thrombus, EMF	Yes	Multiple, watershed area	Steroid, warfarin	No	Alive at 9 months
84	Hameed	2020 [67]	54	M	Pre-syncope	7,600	Secondary HES (T-Cell Lymphoma)	TTE, cardiac MRI, coronary angiography	No	Eosinophilic myocarditis, intramural myocardial tear, thrombus	Yes	Multiple bilateral infarction	PSL, cyclophosphamide	No	Alive
85	Li	2020 [68]	55	F	Right limbs weakness, slurred speech	5,290	Idiopathic HES	Holter ECG, TTE, TEE	No	Unremarkable	No	Multiple acute cerebral ischemic lesions, bilateral middle cerebral artery wall thickening	Antiplatelets, methylprednisolone	No	Alive at 3 months
86	Minupuri	2020 [69]	68	F	Swallowing difficulties, decreased appetite, and generalized weakness	18,820	Idiopathic HES	ECG, TTE, coronary angiography, cardiac MRI	No	LV hypertrophy, global hypokinesis, myocarditis	Yes	Multiple, watershed area	PSL	No	Alive
87	Moalong	2020 [70]	57	F	Neck masses	13,500	Primary HES (FIP1L1/PDGFRA-associated HES)	ND	ND	ND	No	Infarcts on both middle cerebral artery territories	Imatinib	ND	Alive at 2 months
88	Roth	2020 [71]	31	F	Hypersomnolence, rash	8,640	Secondary HES (Drug reaction with eosinophilia and systemic symptoms)	Cardiac MRI	ND	EMF without intracardiac thrombus	Yes	Multiple, watershed area	PSL	No	Alive
89	Ueta	2020 [72]	75	M	Fever, myalgia, hemiplegia	8,744	Secondary HES (EGPA)	ECG, TTE	No	Unremarkable	No	Multiple infarctions in the left posterior limb of the internal capsule	PSL, aspirin, cilostazol	No	Alive at 10 months
90	Barbind	2021 [73]	65	F	Folliculitis of left index finger	68,224	Idiopathic HES	TTE	No	Unremarkable	No	Multiple, watershed area	PSL, hydroxyurea, enoxaparin	No	Alive at 3 months
91	Hwang	2021 [74]	55	M	Cognitive dysfunction, left arm weakness	13,340	Idiopathic HES	ECG, holter ECG, TTE	No	Diastolic dysfunction, mural thrombus	Yes	Multifocal infarctions, subarachnoid hemorrhage, parenchymal hemorrhage	PSL, hidroxyurea, warfarin	No	Alive at 1 month
92	Inaba	2021 [75]	61	M	Numbness of bilateral lower limb	7,930	Secondary HES (EGPA)	TTE, cardiac MRI	No	Delayed myocardial enhancement in the apex area	Yes	Multiple, watershed area	PSL, cyclophosphamide, intravenous immunoglobulin therapy	No	Alive at 7 weeks

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Table 1 (*continued*)

Case	Author	Year [Reference]	Age	Sex	Initial presentation	Eosinophil (/μL)	Cause of hypereosinophlia	Cardiac investigation	Presence of AF	Cardiac findings	Cardiac HES	Cerebral findings	Treatment	Relapse of stroke after treatment	Outcome
93	Jonakowski	2021 [76]	59	M	Spastic triparesis	1,790	Idiopathic HES	ND	ND	ND	ND	Large tumefactive T2-hyperintensive lesion with a partial gadolinium enhancement in the right hemisphere	Methylprednisolone, mepolizumab	No	Alive at 2 years
94	Kiani	2021 [77]	49	F	Dyspnea	2,700	Idiopathic HES	ECG, TTE, cardiac MRI	No	EMF with thrombus	Yes	Multiple infarcts in multiple vascular territories	Methylprednisolone, intravenous immunoglobulin therapy, PSL	No	Alive at 1 year
95	Ling	2021 [78]	74	M	Anxiety	4,100	Secondary HES (SLE)	ECG, TTE	No	Normal systolic function, angina	No	Multiple, watershed area	PSL, cyclophosphamide, hydroxychloroquine, warfarin, clopidogrel	No	Alive at 10 months
96	Lommatzsch	2021 [79]	66	F	Right hemiparesis, aphagia	10,961	Idiopathic HES	ND	Yes	ND	ND	Multiple, watershed area	Methylprednisolone, anticoagulants	No	Alive
97	Mino	2021 [80]	69	F	Left-hand weakness	1,860	Secondary HES (EGPA)	ECG, holter ECG, TTE	No	Unremarkable	No	Multiple, watershed area, small subarachnoid hemorrhaging	PSL, apixaban	No	Alive at 1 year

Note: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; EGPA, eosinophilic granulomatosis with polyangiitis; EMF, endomyocardial fibrosis; F, female; HES, hypereosinophilic syndrome; LV, left ventricle; M, male; MR, mitral regurgitation; MRI, magnetic resonance imaging; ND, not described; PH, pulmonary hypertension; PSL, prednisolone; SLE, systemic lupus erythematosus; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; TR, tricuspid regurgitation.

eosinophilic vasculitis [85,89]. Tissue fibrosis, thrombosis, and/or the extracellular deposition of eosinophil-derived proteins, and predominant eosinophilic infiltration of the vessel wall are observed in damaged vessels of patients with eosinophilic vasculitis. The clinical differences between eosinophilic vasculitis and other types of vasculitis are eosinophilia as well as inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Eosinophilic vasculitis is associated with high blood and/or tissue eosinophilia, but without elevation of ESR and CRP. Conversely, other types of vasculitis may present with a high ESR, a high CRP level, and a normal eosinophilic level [85]. Venous thrombosis is also considered to be an HES-defining feature. Although cases of venous thrombosis occurring due to eosinophil-related diseases have rarely been reported, recent study revealed persistent eosinophilia was associated with relapses of venous thrombosis [89]. These findings were consistent with the results in our review because relapse of stroke was associated with persistent eosinophilia in patients with stroke with HES.

The possible mechanisms of cerebral infarction include hypereosinophilic cardiac thromboembolism from endomyocardial fibrosis, local thromboses due to eosinophil-induced endothelial dysfunction of cerebral vessels, and hypereosinophilic coagulopathy [5,9,21,25,28]. Cerebral infarcts associated with HES have characteristics other than stroke of other etiologies. HES-associated cerebral infarctions are typically multiple and afflict different vascular territories, especially in watershed areas (border zone areas) [37]. This distribution is relatively rare among unselected stroke patients. Classically, watershed infarcts are related to hemodynamic strokes, while cardioembolic strokes are usually territorial. Therefore, watershed infarcts have been well described with episodes of severe, prolonged hypotension, such as those associated with cardiopulmonary arrest; however, they are well seen in patients with HES [17]. In previous studies, consecutive patients with cardioembolic stroke were examined, but border zone strokes were rarely reported [37]. Although cardioembolic stroke often present as multiple bilateral lesions, watershed distribution is not frequently associated with this condition, accounting for less than 10% of cases in a large series of strokes with such distribution [83,90]. Watershed areas refer to hypoperfused vascular territories; thus, low perfusion pressure and related changes in the dynamics of blood flow in the cerebral arteries affect the clearance and destination of embolic particles. Watershed infarcts can be explained by the low capacity of the hypoperfused vessel to eliminate emboli. In addition, blood hyperviscosity can deteriorate the microcirculation and lower the clearance of the microemboli, and eosinophilia can result in elevated blood viscosity. Moreover, eosinophil-derived substances can lead to hypercoagulability through other mechanisms. These reasons can explain why HES-associated cerebral infarctions are typically multiple, especially in watershed areas. Other potential mechanisms of eosinophil-driven endothelial toxicity are eosinophil extracellular traps and phospholipid oxidation. Eosinophil granules contain the cationic proteins major basic protein, eosinophil peroxidase, eosinophil cationic protein, and eosinophil neurotoxin, which induce tissue damage and inflammation. Eosinophils are activated in the setting of atherosclerosis, and they help developing plaque formation. Once arterial thrombosis is triggered, eosinophils are rapidly recruited to the lesion site and intensively interact with platelets causing propagation and stabilization of developing thrombi. Platelets stimulate eosinophils to form eosinophil extracellular traps which in turn induce platelet activation by the major basic protein [91]. Phospholipid oxidation is thought to be another pathway of eosinophil-driven endothelial. Eosinophils combine the abilities of platelets to oxidize and expose distinct prothrombotic aminophospholipids with the capacity of leukocytes to provide tissue factors. Moreover, eosinophils exerted a strong endogenous thrombin-generation capacity that relied on the simultaneous expression of TF and the provision of a procoagulant phospholipid surface that was enriched in 12/15-lipoxygenase–derived oxidized phospholipids. Therefore, oxidation of phospholipids had been suggested to increase their procoagulant potential [92,93].

There is still no definitive therapy for idiopathic HES. Corticosteroids were initially the mainstay of HES treatment and are currently recommended as first-line therapy. Symptomatic patients should be treated with steroid therapy, prednisolone at a dose of 1 mg/kg/day until clinical improvement occurs, after which the dose should be tapered gradually. Symptomatic patients that are nonresponsive to steroids, as defined by the inability to decrease counts of eosinophils, should be offered interferon alpha, pegylated interferon (peg-IFN) alpha, methotrexate, ciclosporin, hydroxycarbamide, imatinib and mepolizumab [94]. Interferon-alpha is recommended for use in HES patients with organ damage and corticosteroid/cytotoxic treatment failure [4]. Interferon alpha activates CD8 T and NK cells leading to suppression of Th2 activity and a decrease in IL-4 and IL-5. In the case of primary (clonal/neoplastic) HES such as FIP1L1/PDGFRA-associated HES, imatinib mesylate can be effective for treatment [51,53,83]. Imatinib mesylate is a specific tyrosine kinase inhibitor with potent inhibiting activity against the Abl and Bcr–Abl protein kinase activity as well as c-kit and PDGFR. Platelet-derived growth factor can lead to activation of eosinophils. Patients with chronic myelomonocytic leukemia that have PDGFR have been reported to respond well to imatinib mesylate [95]. Mepolizumab is an anti-IL-5 recombinant humanised monoclonal antibody. Mepolizumab stops the interaction between IL-5 and its receptor on eosinophils and their progenitors. Therefore, mepolizumab can stabilize the eosinophil count, and the steroid dose could be decreased in patients with HES [96].

HES patients with parasitic infections should undergo antiparasitic therapy. Routine anticoagulation is not recommended unless there is an intracardiac thrombus [97]. It is important to recognize that recurrences of emboli in adequately anticoagulated HES patients are often seen even though anticoagulants or antiplatelets are usually instituted [38].

Cardiac HES is managed by established guidelines for cases of heart failure. Anticoagulation is used if there is an intracardiac thrombus or valve replacement. Most of the literature shows that warfarin is the predominant anticoagulation regimen, and direct acting anticoagulants have not been used significantly in these patients [97].

In summary, our review of reported cases of stroke with HES suggested that the characteristics of most cases are multiple infarctions in the watershed area, and cardiac HES is not always associated with stroke. Steroid therapy should be administered to treat stroke in idiopathic HES patients as a first-line therapy for the treatment of stroke as well as control of eosinophilia.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100915.

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