Diagnosis and Outcome of Patients with Idiopathic Hypereosinophilic Syndrome and Cardiac Involvement

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INTRODUCTION

- The diagnosis of **idiopathic hypereosinophilic syndrome (iHES)** is based on three major criteria: i) peripheral blood (PB) **eosinophilia ≥ 1.5 x 10^9/L** for > 1 month, ii) signs of **eosinophilic organ or tissue infiltration**, and iii) **exclusion of secondary causes**.[1]
- The clinical presentation of iHES is widely heterogeneous and varies in the pattern and extent of organ damage. In cases with multi-organ involvement (e.g. lung, cardiac, gastrointestinal, cutaneous manifestations), the **main differential diagnosis is eosinophilic granulomatosis with polyangiitis** (EGPA, formerly known as Churg-Strauss syndrome), an antineutrophil cytoplasmic autoantibodies (ANCA)-associated systemic vasculitis.[2]
- iHES or ANCA-negative EGPA **may lead to cardiac involvement (CI) in up to 60%** of affected patients and has a potential **impact on morbidity and mortality**.[3-5] The different disease stages include an acute phase with eosinophilic myocarditis and myocardial necrosis which is followed by a subacute phase with formation of thrombi and a final phase of fibrotic replacement and restrictive cardiomyopathy.[6-10] **CI often occurs early** in the course of iHES and EGPA and is reported to be more common in ANCA-negative than ANCA-positive EGPA patients.[11] The onset of restrictive cardiomyopathy is associated with early death.[12]

STUDY OBJECTIVES AND DESIGN

- Because of the heterogeneous presentations, **specific guidelines for assessment of cardiac involvement in iHES are lacking**. Basic information is provided by clinical investigation, electrocardiography and cardiac biomarkers, e.g., N-terminal prohormone B-type natriuretic peptide (NT-proBNP), and troponin I.
- Conventional transthoracic echocardiography **(TTE) and endomyocardial biopsy have long been recognized as the diagnostic standard procedures**. However, the **sensitivity of TTE** in early detection of myocardial infiltration/fibrosis is **highly variable** (range: 23-83%),[11] while **endomyocardial biopsy** is invasive and **frequently non-informative** (due to limitations in samples size and accessible biopsy sites).[9]
- **Cardiac magnetic resonance imaging** (MRI) has emerged as useful imaging modality. It **reliably provides data** on structural changes, particularly with the use of **late gadolinium enhancement** (LGE) as a **marker for infiltration/fibrosis, thrombi or pericardial effusion**. **MRI can also detect functional changes,** including dysfunction of heart valves or impairment of left ventricular ejection fraction (LV-EF).
- Given the limited information available on CI in patients with iHES, we sought to **evaluate the diagnosis and outcome of CI through a combination of cardiac MRI and cardiac biomarkers in a large series of iHES patients** within the German Registry on Eosinophils and Mast Cells (GREM).

Figure 1: Patient flowchart

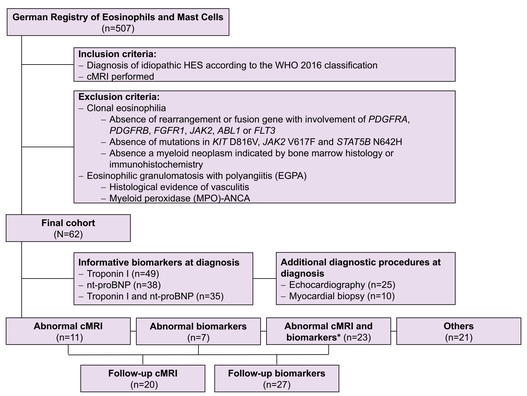
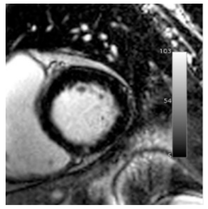
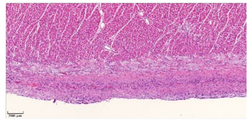


Figure 2: Assessment of cardiac involvement





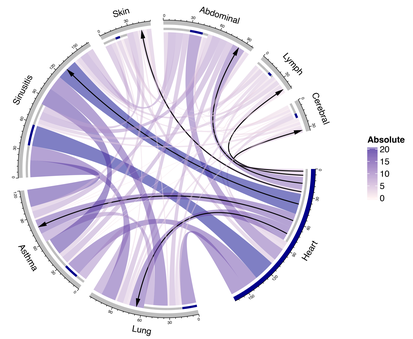
Autopsy (above): Endocardium with subendothelial fibrosis

Cardiac MRI (left): Late gadolinium enhancement

- Diagnosis of **CI by cardiac MRI was based on** detection of a non-ischaemic intramyocardial **LGE, LV-EF <50%, presence of intracavitary thrombi**, moderate to severe **valvular heart disease**, **conduction disorder, or pericardial effusion >10mm in the absence of other causes** (e.g., coronary artery disease, cardiomyopathy, hypertensive heart disease, perimyocarditis).
- PB counts including absolute and relative numbers of eosinophils were evaluated in all patients. Glomerular filtration rate-corrected **NT-proBNP** (normal range: 0-125 ng/l) and **troponin I** (normal range: 0-0.045 µg/l) **were measured at diagnosis and during follow-up** as clinically indicated.

RESULTS

Figure 3: Multi-organ involvement



- **Organ involvement.** At diagnosis, patients revealed involvement of **lungs** (26/62, **42%**), **asthma** (23/62, **37%**), **paranasal sinuses** (31/62, **50%**), **abdominal organs** (bowel, liver, spleen, 25/62, **40%**), **skin** (15/62, **24%**), **lymph nodes** (10/62, **16%**), **brain** (5/62, **8%**) and **other locations** (joints/muscles, 8/62, **13%**). Overlapping involvement of two or more organs was observed in 52/62 (**84%**) patients.

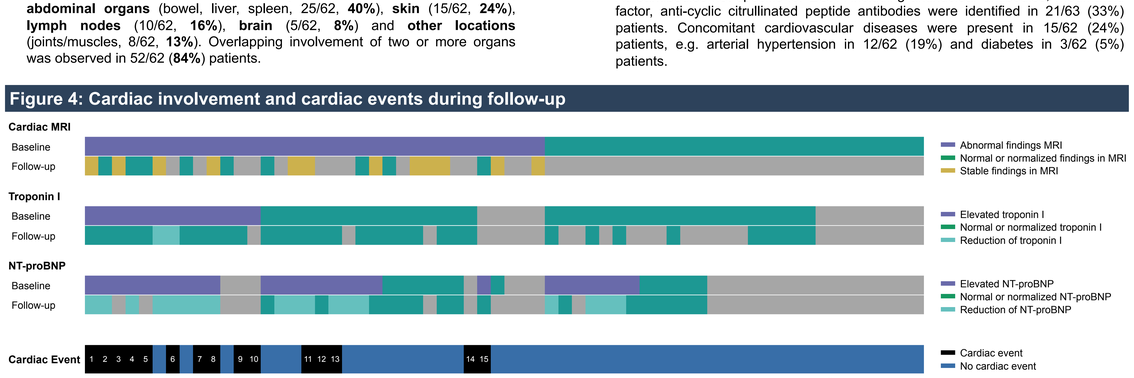
Table 1: Disease and treatment characteristics

	Abnormal cardiac MRI (n=34)	Abnormal biomarkers (n=30)	Abnormal MRI and biomarkers (n=23)	No abnormal MRI or biomarkers (n=21)
Cardiac MRI				
Presence of LGE, n (%)	31 (91)	23 (77)	23 (100)	0 (0)
Intracavitary thrombi, n (%)	6 (18)	4 (13)	4 (17)	0 (0)
Pericardial effusion, n (%)	11 (32)	7 (23)	7 (30)	0 (0)
Involvement of heart valves/ conduction system, n (%)	9 (26)	7 (23)	7 (30)	0 (0)
LV-EF (%), median (IQR)	59 (50-64)	59 (52-65)	58 (49-63)	64 (59-69)
Impaired LV-EF (< 50%), n (%)	9 (26)	7 (23)	7 (30)	0 (0)
LV-GLS (%), median (IQR)	-11 (-14-[-]10)	-11 (-13-[-]9)	-11 (-13-[-]10)	-15 (-16-[-]12)
Cardiac biomarkers, median (IQR)				
NT-proBNP (ng/l)	631 (129-1846)	602 (223-1788)	827 (350-2069)	51 (40-92)
Troponin I (µg/l)	0.02 (0.02-0.14)	0.02 (0.02-0.14)	0.08 (0.02-0.15)	0.02 (0.02-0.02)
Organ involvement, n (%)				
Lung	16 (47)	16 (53)	13 (57)	7 (33)
Asthma	16 (47)	15 (50)	13 (57)	5 (24)
Paranasal sinuses	23 (68)	22 (73)	17 (74)	3 (14.0)
Skin	5 (15)	6 (20)	4 (17)	9 (43.0)
Gastrointestinal tract or intraabdominal organs (spleen, liver, kidney)	14 (41)	11 (37)	8 (35)	8 (38.0)
Lymph nodes	4 (12)	3 (10)	2 (9)	5 (24.0)
Brain	5 (14)	4 (13)	4 (17)	0 (0)
Others	2 (6)	2 (7)	2 (9)	6 (29.0)
Immunosuppresive therapy, n (%)				
Glucocorticoids	34 (100)	30 (100)	23 (100)	19 (91)
Mepolizumab	13 (38)	10 (33)	9 (39)	0 (0)
Azathioprine	11 (32)	10 (33)	8 (35)	0 (0)
Cyclophosphamide	9 (27)	9 (30)	9 (39)	1 (5)
Methotrexate	9 (27)	9 (30)	7 (30)	0 (0)
Others	2 (6)	2 (7)	1 (4)	2 (10)
Follow-up				
Cardiac events during follow-up, n (%)	15 (44)	14 (47)	14 (61)	0 (0)
Follow-up cardiac MRI, n (%)	20 (59)	15 (50)	15 (65)	0 (0)
Regression of LGE intensity or extent	7	7	7	0
Thrombus regression	1	1	1	0
Improvement of LV-EF	1	0	0	0
Follow-up biomarkers				
NT-proBNP (ng/l), median (IQR)	139 (68-352)	206 (99-476)	313 (103-518)	79 (57-114)
Troponin I (µg/l), median (IQR)	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.01 (0.01-0.01)

Abbreviations: IQR, interquartile range; LGE, late gadolinium enhancement; LV-EF, left ventricular ejection fraction; LV-GLS, left ventricular global longitudinal strain; MRI, cardiac magnetic resonance imaging; n, numbers; NT-proBNP, N-terminal prohormone B-type natriuretic peptide

Basic characteristics. Median age at diagnosis and at cardiac MRI were 49 (IQR 37-58; range 15-88) and 51 (IQR 40-63; range 25-88) years, respectively. There was a slight male predominance (36/62 [58%]). Eosinophilia ≥1.5x10^9/L in PB was present in all patients (median 4.5x10^9/L, IQR 2.8-9.5; range 1.5-94.4). Autoantibodies not specific for EGPA including antinuclear antibodies, rheumatoid factor, anti-cyclic citrullinated peptide antibodies were identified in 21/63 (33%) patients. Concomitant cardiovascular diseases were present in 15/62 (24%) patients, e.g. arterial hypertension in 12/62 (19%) and diabetes in 3/62 (5%) patients.

Figure 4: Cardiac involvement and cardiac events during follow-up



Cardiac events included cardiovascular death, cerebral embolism, onset of arrhythmia, severe heart disease requiring surgery, hemodynamically relevant pericardial effusion, presence of intracavitary thrombi, or manifestation of LV heart failure

CONCLUSIONS

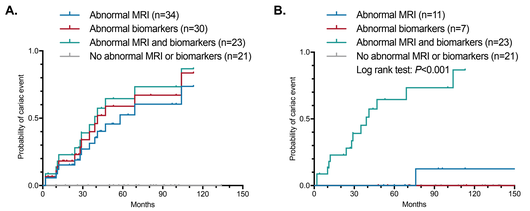
- **Cardiac involvement is a common and potentially under-diagnosed manifestation of iHES.**
- **Cardiac MRI is a sensitive and reliable technique for detection of cardiac involvement in iHES; the presence of late gadolinium enhancement is a particularly useful disease marker.**
- **Cardiac biomarkers should be included in the assessment, as the combination of elevated biomarkers and a pathological cardiac MRI was associated with an increased risk of cardiac events.**
- **Cardiac MRI and biomarkers can serve as parameters for response assessment.**
- **Limitations of our study:**
  - **lack of clear definitions for diagnosis of cardiac involvement in iHES (missing validated definition or gold standard).**
  - **risk of over- or under-interpretation of the extent of cardiac involvement based on the definition used in this study.**

Table 2: Troponin I and NT-proBNP

	All patients with iHES and cardiac MRI (n=62)
Cardiac biomarkers	
Available cardiac biomarker data	50/62 (81)
Elevated cardiac biomarkers	30/50 (60)
Available NT-proBNP	38/62 (61)
NT-proBNP (ng/l)	265 (103-1165)
NT-proBNP > 125 ng/l	27/38 (43)
	631 (212-1730)
Available troponin I (µg/l), n (%)	49/62 (78)
Troponin I (µg/l)	0.015 (<0.015-0.026)
Troponin I > 0.045 µg/l, n (%)	10/49 (20)
	0.02 (0.02-0.13)
Both biomarkers available, n (%)	37 (60)
Both cardiac biomarkers elevated	10/37 (27)

Abbreviations: iHES, idiopathic hypereosinophilic syndrome; MRI, cardiac magnetic resonance imaging; n, numbers; NT-proBNP, N-terminal prohormone B-type natriuretic peptide

Figure 5: Cumulative risk of a cardiac event



- **A.-B.** Cox proportional hazards regression analyses to predict the risk for a cardiac event in iHES patients by means of cardiac magnetic resonance imaging (MRI) and biomarkers (troponin I and NT-proBNP). **A. Patients** were **attributable to more than more group**. **B. Patients** were **attributable to only one group** (distinct patient groups).

Treatment

- Almost all patients with cardiac involvement received **glucocorticoid-based treatment** (60/62, **97%**).
- Three-quarters of patients (36/48, 75%) were also treated with the anti-IL-5 agent **mepolizumab** (13/48, **27%**) or immunosuppressive agents, such as **azathioprine** (15/48, **31%**), **cyclophosphamide** (10/48, **21%**), **methotrexate** (12/48, **25%**), **mycophenolate mofetil or interferon-alpha** (7/48, **15%**).

References

1. Roufosse et al., J Allergy Clin Immunol 2010. **2.** Chang et al., J Allergy Clin Immunol Pract 2021. **3.** Ommen et al., Am J Cardiol 2000. **4.** Ogbogu et al., Immunol Allergy Clin North Am 2007. **5.** Cereda et al., Eur J Intern Med 2017. **6.** Mankad et al., Heart 2016. **7.** Shah et al., Echocardiography 2006. **8.** Bishop et al., Circulation 2001. **9.** Salanitri et al., AJR Am J Roentgenol 2005. **10.** Corradi et al., Hum Pathol 2004. **11.** Mavrogeni et al., Inflamm Allergy Drug Targets 2014. **12.** Kleinfeldt et al., Clin Res Cardiol 2010.

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