NEUROLOGIC MANIFESTATIONS OF HYPEREOSINOPHILIC SYNDROME – REVIEW OF THE LITERATURE

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SUMMARY – Hypereosinophilic syndrome is a rare disorder of the hematopoietic system. The disease is characterized by continuously high number of eosinophils (>1.5x10^9/L) for more than six months. Other possible causes of hypereosinophilia, such as allergic and parasitic diseases, malignant disease, Churg-Strauss disease and infection should be eliminated. The most common manifestations of hypereosinophilic syndrome are pulmonary, skin, gastrointestinal, cardiac difficulties and neurologic lesions. Numerous neurologic lesions have been described, in particular of the central and peripheral nervous systems. Review of the literature revealed the following to have been recorded so far: mononeuritis multiplex, sensory polyneuropathy, radiculopathy, myalgia, myositis and perimyositis, neuropathy, ataxia, paraplegia, ophthalmologic abnormalities, optic neuritis, hemiplegia-hemiparesis, spasmodic quadriplegia, seizures, meningitis, cerebral infarction, organic psychosyndrome, other mental changes, stroke, temporal arteritis, leptomeningeal dissemination, memory deficits and dysarthria.

Key words: *Manifestations, neurologic; Hypereosinophilic syndrome*

Introduction

Hypereosinophilic syndrome (HES) is a rare and heterogeneous group of disorders defined as persistent marked blood eosinophilia (>1.5x10^9/L for more than six consecutive months) associated with evidence of eosinophil-induced organ damage, where other causes of hypereosinophilia such as allergic, parasitic, and malignant disorders have been excluded[1-4]. The prevalence is unknown, younger to middle-aged patients are most frequently affected, with a male predominance (4-9:1 ratio)[5]. HES is a disease of multifactorial genesis, from clonal tumorous proliferation to reactive changes. The myeloproliferative variant caused by interstitial deletion in chromosome 4q12 and the lymphoproliferative variant associated with clonal proliferation of phenotypically abnormal T cells have been differentiated. An autosomal dominant familial form that has been mapped to chromosome 5q31, episodic form (Gleich's syndrome) and a clinically silent or benign form have also been described. In patients with the myeloproliferative variant, well responding to imatinib therapy, FIP1L1/PDGFRA (F/P) has been identified, being deemed an imatinib responsive HES. The lymphoproliferative variant HES (L-HES) is characterized by a phenotypically distinct clonal T cell population in peripheral blood. Hypereosinophilia is a consequence of the increased production of the eosinophilopoietic cytokine, especially interleukin 5 (IL-5). Diagnosis is based on establishing a population of T cells with an aberrant phenotype, most often $CD3^-CD4^+CD8^-$ in peripheral blood. However, around 50% of patients with HES can be classified as neither myeloproliferative nor lymphoproliferative variant[6-13].

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HES is treated by steroids, cytotoxic agents, immunomodulatory therapies, tyrosine kinase inhibitors, monoclonal antibody therapy and bone marrow transplantation[6-8].

The organs affected by hypereosinophilia differ from case to case. Most commonly, these are the skin, heart, lungs, central and peripheral nervous systems. Frequent manifestations are also hepato- and/or splenomegaly, eosinophilic gastroenteritis, coagulation disorders, etc.[14-17]. Neurologic symptomatology is nonspecific and varies; therefore we are presenting here the neurologic manifestations of HES recorded so far.

Review of the Literature and Discussion

We performed systematic review of peer-reviewed publications identified through MEDLINE databases (searched in May 2011). The search term was Hypereosinophil syndrome, and the search was limited to clinical trials and articles in English. The search was extended by reviewing bibliographies from pertinent original reports of data and review articles. Unpublished trials and data presented only in abstract form are not included.

Literature reports damages to the central nervous system and peripheral nervous system. Authors very

Table 1. Neurologic manifestations of the hypereosinophilic syndrome

Authors	Neurologic manifestations
Gardner-Thorpe *et al.*[18]	
Delaporte *et al.*[19]	Optic ataxia, paralysis of visual fixation
Farcet *et al.*[20]	Hemiplegia, spasmodic quadriplegia, seizures
Chaine *et al.*[21]	Arterial occlusions of the retina, neurologic signs
Kessler *et al.*[22]	Blurred vision on one or both eyes
Moore *et al.*[23]	Neurologic disturbances
	Central nervous system dysfunction, encephalopathy characterized by behavioral disturbances, motor neuron signs, peripheral neuropathy with sensory polyneuropathy, mononeuritis multiplex, radiculopathy
Weingarten *et al.*[24]	Meningitis
Martin-González *et al.*[25]	Neurologic dysfunction
Zagami *et al.*[26]	Ataxia-telangiectasia
Haraoka *et al.*[27]	Hemiparesis
Kumara *et al.*[28]	Neurologic deficit
Otto[29]	Frequent neurologic signs, cerebral infarction, organic psychosyndrome
	Abnormalities of the central and peripheral nervous system
Lee *et al.*[30]	Mononeuritis multiplex (acute myelino-axonal degeneration with endoneural
Arnaud *et al.*[31]	edema), myalgia, axonal pattern of neuropathy
	Bilateral papilledema
Koto *et al.*[32]	Perimyositis, myositis, myalgia
Pellissier *et al.*[33]	Peripheral neuropathy, mental changes
Cengiz *et al.*[34]	Visual and cognitive disorders
Prunier *et al.*[35]	Paraplegia, dysuria
Endo and Miyake[36]	Ataxia, memory deficits, dysarthria
Wolf *et al.*[37]	Optic neuritis
Lincoff and Schlesinger[38]	Cerebral sinus thrombosis, cerebral hemorrhage
Numagami *et al.*[39]	Sciatic neuropathies
Srinavasan *et al.*[40]	Stroke, hemiplegia
Noureen and Rana[41]	Stroke
Perini *et al.*[42]	Stroke
Sethi and Schmidley[43]	Temporal arteritis
Ito *et al.*[44]	Leptomeningeal dissemination, intraventricular mass lesion
Kanamori *et al.*[45]	

often report numerous associated detrimental effects manifested by a number of symptoms such a mononeuritis multiplex, sensory polyneuropathy, radiculopathy, myalgia, myositis and perimyositis, neuropathy, ataxia, paraplegia, ophthalmologic abnormalities, optic neuritis, hemiplegia-hemiparesis, spasmodic quadriplegia, seizures, meningitis, cerebral infarction, organic psychosyndrome and other mental changes, memory deficits, dysarthria, etc. (Table 1).

HES appears to be a very rare disease, manifested in damages to a number of organs. Most often affected are the skin, heart, lungs, central and peripheral nervous systems, in as many as 50% of cases[1]. Diffuse encephalopathy presents as altered behavior and cognitive function, confusion, and memory loss. Peripheral neuropathies present as symmetric or asymmetric sensory changes, pure motor deficits, or mixed sensory and motor complaints. Stroke or transient ischemic episodes may result from cardiac difficulties and heart originating thrombus, but also from increased inclination to thrombosis[1,2,38]. It is the increased inclination to thrombosis in HES that probably causes thrombosis of intracranial veins (longitudinal and/or lateral sinus).

Thus, hypereosinophilic syndrome may result in a number of neurologic signs. Therefore, in cases of neurologic signs with no clinically established cause, especially in younger people, the possible HES should be considered.

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Sažetak

NEUROLOŠKE MANIFESTACIJE HIPEREOZINOFILNOG SINDROMA – PREGLED LITERATURE

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Hipereozinofilni sindrom je rijetka bolest hematopoetskog sustava. Bolest je obilježena visokim brojem eozinofila (>1,5x10^9/L) duže od šest mjeseci, uz uvjet da su isključeni drugi mogući uzroci hipereozinofilije kao što su alergija i parazitne bolesti, maligne bolesti, Churg-Straussova bolest i druge infekcijske bolesti. Većina kliničkih manifestacija hipereozinofilnog sindroma obuhvaća oštećenja pluća, kože, probavnog sustava, srčane poremećaje i neurološka oštećenja. Opisana su brojna neurološka oštećenja središnjeg i perifernog živčanog sustava. Pretraživanjem literature nalaze se moguće neurološke manifestacije bolesti kao što su *mononeuritis multiplex*, senzorna polineuropatija, radikulopatija, mijalgija, miozitis i perimiozitis, neuropatija, ataksija, paraplegija, oftalmološki poremećaji, optički neuritis, hemiplegija-hemipareza, spastička tetraplegija, epileptični napadaji, meningitis, ishemijski moždani udar, psihoorganski sindrom i drugi mentalni poremećaji, temporalni arteritis, leptomeningealna diseminacija, poremećaji pamćenja i dizartrija.

Ključne riječi: *Manifestacije, neurološke; Hipereozinofilni sindrom*