Göteborg, 2023

Inclusion body myositis
Genetic, clinical, and epidemiological aspects

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hjärtats Aula, Vita Stråket 12, Sahlgrenska Universitetssjukhuset, Göteborg, fredagen den 9 juni 2023, klockan 9.00.

av Ulrika Lindgren

Fakultetsopponent:
Professor Werner Stenzel
Charité – Universitätsmedizin Berlin, Germany

Avhandlingen baseras på följande delarbeten

I. Lindgren U, Roos S, Hedberg-Oldfors C, Moslemi A-R, Lindberg C, Oldfors A. Mitochondrial pathology in inclusion body myositis.
Neuromuscular Disorders, 2015;25(4):281-288.

II. Hedberg-Oldfors C, Lindgren U, Basu S, Visuttijai K, Lindberg C, Falkenberg M, Larsson Lekholm E, Oldfors A. Mitochondrial DNA variants in inclusion body myositis characterized by deep sequencing.
Brain Pathology, 2021;31(3):e12931.

III. Lindgren U, Pullerits R, Lindberg C, Oldfors A. Epidemiology, survival, and clinical characteristics of inclusion body myositis.
Annals of Neurology, 2022;92(2):201-212.

IV. Lindgren U, Hedberg-Oldfors C, Pullerits R, Lindberg C, Oldfors A. Inclusion body myositis with early onset – a population-based study.
Manuscript.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

GÖTEBORGS UNIVERSITET

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Inclusion body myositis
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Abstract

The inflammatory myopathy inclusion body myositis (IBM) is characterized by progressive muscle weakness and dysphagia in individuals over 45 years of age. Muscle biopsy shows inflammatory infiltrates, vacuoles with protein accumulation and cytochrome c oxidase (COX)-deficient muscle fibers. Multiple rearrangements are seen in mitochondrial DNA (mtDNA) in muscle. Inclusion body myositis is rare and larger population-based studies few. The aim of this thesis was to describe aspects of IBM in a population-based cohort in Region Västra Götaland (VGR), Sweden, from 1985 to 2017. Methods included analysis of muscle biopsies, DNA analysis, and review of medical records.

The relative amount of mtDNA deletions in muscle was associated with the amount of COX-deficient muscle fibers ($p<0.001$) in 26 patients (Paper I). Mean mutation load in muscle mtDNA was 10% (range 1-35%) in 21 patients with IBM and 1% (range 0.2-3%) in controls (Paper II). We saw no increase in variants in nuclear genes associated with mitochondrial myopathies and multiple mtDNA deletions (Papers I, II, IV).

Including 128 patients fulfilling strict diagnostic criteria, the prevalence of IBM December 31, 2017, was 32 per million inhabitants in VGR (19 per million women and 45 per million men). Mean incidence was 2.5 per million inhabitants and year. Cumulative survival was moderately decreased. The most common first symptom was quadriceps weakness. Dysphagia occurred in 77% and autoantibodies to cytosolic 5'-nucleotidase 1A were present in 40% of patients (Paper III). Six additional patients were <46 years of age at symptom onset. They had reduced survival, progressive muscle weakness, high frequencies of swallowing difficulties and ventilation assistance and high mtDNA mutation load compared with controls (Paper IV).

In conclusion, IBM is a severe inflammatory myopathy that reduces cumulative survival. Patients are affected by progressive muscle weakness, dysphagia, and COX-deficiency caused by high levels of mtDNA rearrangements.

Keywords: inclusion body myositis, mitochondrial DNA, epidemiology, cytochrome c oxidase, inflammatory myopathy

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