Genetic aspects of Sterno-costo-clavicular hyperostosis

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• To construct the pedigree of patients with SCCH with special attention to the presence of other inflammatory disorders such as inflammatory bowel disease, psoriasis, inflammatory arthritis in patients and kindreds.• To identify the gene mutation...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bone disorders (excl congenital and fractures)
Study type	Observational invasive

Summary

ID

NL-OMON31999

Source
ToetsingOnline

Brief title
Genetics of SCCH

Condition

- Bone disorders (excl congenital and fractures)

Synonym
chronic sterile inflammation of the anterior chest wall

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: CRMO, Genetic mutations, SAPHO syndrome, Sterno-costo-clavicular hyperostosis

Outcome measures

Primary outcome

Genetics mutations in SCCH

Secondary outcome

Degree of occurence of auto-inflammatory disorders in patients with SCCH and

their kindreds

Study description

Background summary

Sternocostoclavicular hyperostosis (SCCH) is a relatively rare inflammatory disorder of the axial skeleton presenting with pain, tenderness and swelling of the sternum, medial ends of the clavicles and upper ribs, with the spine and mandible being less commonly affected. The disease may start in early adulthood and lasts several years with a natural course characterized by periods of exacerbations and remissions. Pathophysiologically, the bone lesions are due to a chronic sterile osteomyelitis of unknown aetiology leading to hyperostosis of bone in the anterior chest wall. This reflects abnormal osteogenesis and is radiologically manifested as sclerosis, with bony enlargement and increased bone density. The mixture of destructive and proliferative components is similar to classic psoriatic arthropathy and seronegative spondylarthropathies, but the unusual locations and the variability of bone involvement leads to a wide range of differential diagnoses including arthritis, osteomyelitis, Paget*s disease of bone, primary bone tumors, and metastases. SCCH remains a largely unrecognized syndrome, partly because of its limited manifestations as it misses some of the essential components of the more severe form of chronic sterile osteomyelitis of adults: the SAPHO syndrome (Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis), and partly because of its waxing and waning natural course.

Although bone is the primary inflammation target, the disease has been described in association with pustulosa-palmo-plantaris or other chronic inflammatory disorders of the skin such as psoriasis and also with inflammatory gut disorders such as Coeliac disease or Crohn*s disease (16). The

pathophysiology of SCCH and its more severe form SAPHO remains largely enigmatic. Chronic Recurrent Multifocal Osteomyelitis (CRMO) is the childhood form of chronic sterile osteomyelitis, characterized by multifocal bone lesions, with multiple recurrent episodes of bone inflammation not responding to prolonged antimicrobial therapy. The inflammatory bone lesions are not confined to the axial skeleton like in SCCH or SAPHO but are typically located at the metaphyses of tubular long bones. Recent evidence suggests that the etiology of sporadic CRMO has a genetic component, including several reports of affected siblings, affected parent and child duos, concordant monozygotic twins, with a CRMO susceptibility locus mapped to human chromosome 18q21.3-18q22. In addition, as many as half of patients have a first-degree or second-degree family member who is affected by a chronic inflammatory disorder, most commonly psoriasis. 2 The genes responsible for an autosomal recessive rare form of chronic recurrent multifocal osteomyelitis (CRMO) with a more severe phenotype (earlier presentation ~ 2 years of age, more frequent recurrences, shorter remissions, poor linear growth and disease continuing in adulthood) called Majeed syndrome (LPIN2), for cherubism (SH3BP2 and possibly PTPN11), a hereditary chronic inflammatory disorder in which bone is also the primary inflammatory target and for murine chronic multifocal osteomyelitis, an autosomal recessive mouse model of CRMO with a locus mapped to a 21 cM region of murine chromosome 18 (missense mutation in the pstpip2 gene) have also been recently identified.

The role for genetic factors in SCCH is further supported by a fortuitously discovered mouse model derived from a BALB/c.DBA/2 strain. The mice spontaneously develop chronic multifocal aseptic osteomyelitis similar to the bone lesions seen in humans with SAPHO syndrome. The susceptibility gene, which is located on chromosome 18 (at a locus designated *cmo* for chronic multifocal osteomyelitis) transmits the disease according to a recessive pattern. Analysis of the cmo locus showed a missense mutation on gene pstpip2 (praline-serine-threonine phosphatase-interacting protein 2). The pstpip proteins are involved in regulating the immune response via several mechanism mediated by T cells and apoptosis. Several groups are currently investigating the potential role for pstpip2 in a number of chronic inflammatory diseases, including psoriasis. Not substantiated in a cohort of 89 patients with non-bacterial osteitis which included patients with CRMO (Jansson 2007). Furthermore, a study conducted in Germany in a cohort of 27 patients with chronic recurrent multifocal osteomyelitis (a form of SAPHO) and their parents suggests a role for a dominantly inherited gene with variable penetrance, also located on chromosome 18q, near the D18S60 marker.

SCCH is a rare disease associated with significant morbidity that illustrates the need for educational efforts aimed at improving the diagnosis and treatment of affected patients and at accumulating knowledge on the disease. SCCH also presents a unique model of a potential autoinflammatory disorder of the skeleton, likely to be due to a genetically influenced disorder of innate immunity. Unraveling the specific genetic factors involved in the pathogenesis

of this disorder would contribute to our understanding of the complex interface of the immune system with the skeleton.

Study objective

• To construct the pedigree of patients with SCCH with special attention to the presence of other inflammatory disorders such as inflammatory bowel disease, psoriasis, inflammatory arthritis in patients and kindreds.
• To identify the gene mutation responsible for the abnormal inflammatory response in SCCH, starting with the already identified mutations in children with CRMO, Cherubism and Majeed syndrome and the mutations identified in the mice models of CRMO and in the TNF-alpha gene.

Study design

Open study design, with retrospective analysis of data at diagnosis of SCCH and prospective pedigree construction and genetic analysis of DNA obtained at some stage during the natural course of the disease.

Study burden and risks

Patients participation involves one visit to the outpatient departement of the LUMC during which an interview of about one hour duration will be conducted, following which blood will be collected and stored for future DNA analysis.
The above procedure can also be conducted at the patients home would she or he so prefer.
No risks are involved.
Were indicated DNA will also be collected, based on the patient pedigree, from relevant family members by appointment after singing informed consent.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Established diagnosis of SCCH on the basis of clinical, scintigraohic and radiologic findings

Exclusion criteria

The unwillingness of the patient to participate in the study

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-09-2008
Enrollment:	50

Type:	Actual

Ethics review

Approved WMO Date:	16-09-2008
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	13-09-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL23310.058.08