

## Sarcoidosis and acquired type II-b hyperlipoproteinaemia

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**ABSTRACT:** In four of eleven patients with histologically-proven sarcoidosis (stage II or III), type II-b hyperlipoproteinaemia (HLP) with increased levels of total cholesterol, triglycerides and low density lipoprotein, and a decreased level of high density lipoprotein was observed. These results suggest that type II-b HLP may be associated with sarcoidosis with systemic sarcoid infiltration (stage II or III).

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Sarcoidosis is a granulomatous disorder of unknown cause with multisystem involvement [1, 2]. The pathogenesis of sarcoidosis has not been established. Hyperlipoproteinaemia (HLP) is defined as excess concentrations of lipoproteins, which transport cholesterol (Cho) and triglycerides (TG), in the bloodstream. Clinical recognition of HLP is unknown; sarcoidosis accompanying HLP has not been reported. In this report, possible relationships between sarcoidosis and HLP are discussed.

### Subjects and methods

Thirty-six patients (22 women and 14 men; mean age 45yrs) were admitted because of sarcoidosis between 1973 and 1986. The diagnosis of sarcoidosis was made by lymph node biopsy, the Kveim-Siltzbach test, clinical signs and/or laboratory data. Among the 36 patients, 4 had cervical lymphadenopathy, 21 manifested roentgenographic stage I sarcoidosis, 9 stage II, and 2 stage III. Measurement of serum Cho was used as a screening test in all 36 patients, none of whom had received steroid therapy prior to admission.

The patients were studied under metabolic ward conditions on a diet of 70-75 g of proteins, 45 g of lipids and 320 g of carbohydrates. Blood lipid analyses were performed in all patients prior to steroid therapy. Venous blood samples were drawn under stable fasting conditions each morning. Serum total Cho and plasma TG were measured automatically. Free fatty acids, phospholipids and low density lipoprotein (LDL) were determined with an assay kit (Nihon Shyoji Co., Osaka). Lipoprotein electrophoresis was performed by the agarose gel method, and measurement of lipoprotein sub-fractions was carried out by ultracentrifugation and manganese chloride (MnCl<sub>2</sub>) precipitation. Eight-

een healthy volunteers were selected as normal subjects (controls).

### Results

In four of the patients who showed sarcoidosis stage II or III, serum Cho levels were significantly elevated (mean±SD, 261±26 mg·dl<sup>-1</sup>; p<0.01), compared with (170±21 mg·dl<sup>-1</sup>) in normal controls (NC). In these four patients, further detailed lipid analyses were performed. Levels of TG (233±65 mg·dl<sup>-1</sup>; p<0.01) and LDL (888±92 mg·dl<sup>-1</sup>; p<0.01) in these patients were significantly increased compared with NC (95±24 and 458±50 mg·dl<sup>-1</sup>, respectively). The percentage of high density lipoprotein (HDL, 15.4±1.0%; p<0.01) in the four patients was significantly decreased compared with (25.7±7.7%) in NC, and lipoprotein electrophoresis revealed type II-b HLP. In contents of free fatty acids (469±88 vs 418±68 μEq·l<sup>-1</sup>), phospholipids (234±44 vs 189±21 mg·dl<sup>-1</sup>) and HDL-Ch (44 mg·dl<sup>-1</sup> n=2 vs 47±7; n=2) mg·dl<sup>-1</sup>; n=2), however, there were no significant differences between sarcoidosis patients and NC. The four patients all had pulmonary infiltrations and/or fibrosis related to systemic sarcoidosis.

### Discussion

Our study presents a possible connection of HLP with systemic sarcoidosis. Seventeen patients had prednisolone administered after admission because of progressive pulmonary involvement or involvement of vital organs. In thirteen patients without HLP on admission, steroids produced a mild hypercholesterolaemia, but this pathological state immediately disappeared after the tapering-off of steroids. In our mass survey of 199 rural males (mean age 51.9 yrs) and 108 rural females

(mean age 53.7 yrs) from the Okayama area, who had no underlying diseases (including atherosclerosis, hypertension, cardiac diseases and diabetes mellitus) frequency of hypercholesterolaemia (more than  $170 \pm 2SD$  mg-dl<sup>-1</sup>) was 18 males (9.0%) and 12 females (11.1%), and frequency of hypertriglyceridaemia (more than  $95 \pm 2SD$  mg-dl<sup>-1</sup>) was 26 males (13.1%) and 11 females (10.1%). In Japan, mass surveys have shown that frequencies of hypercholesterolaemia range from 11–13% and those of hypertriglyceridaemia from 9–12% in rural Japanese people without underlying diseases [3]. These results suggest that the frequency of HLP may be higher in patients with severe sarcoidosis (stage II or III) than age-matched normal Japanese subjects.

Although the pathophysiology of HLP occurring in systemic (severe) sarcoidosis, a multisystem disorder with noncaseating granulomatous lesions, is unclear at present, it is speculated that, in the affected organs, some conformational changes in the surface membrane of inflammatory cells (mononuclear cells and macrophages) and fibroblasts may occur after granulomatous changes. Subsequent fibrosis induced by these cells may then cause the impairment of LDL-specific receptor functions in these peripheral cells, resulting in disturbances of LDL catabolism, which is mediated by LDL and scavenger (inflammatory-cell) pathways [4, 5]. This may result in HLP. It is of great interest that such HLP was observed in severe sarcoidosis with pulmonary fibrosis and/or the involvement of other vital organs. However, for a better understanding of the HLP occur-

ring with sarcoid changes, further studies, *i.e.* receptor assays of inflammatory cells and fibroblasts around the granulomatous lesions, should be attempted.

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RÉSUMÉ: Chez quatre de onze patients atteints de sarcoïdose prouvée histologiquement et de stade II ou III, une hyperlipoprotéïnémie de type II-b, avec des taux élevés de cholestérol total, de triglycérides et de lipoprotéïnes à faible densité, ainsi qu'une diminution des lipoprotéïnes de haute densité, ont été observées. Ces résultats suggèrent que l'hyperlipoprotéïnémie de type II-b peut être associée à la sarcoïdose comportant une infiltration sarcoïde systémique de stade II ou III.