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*Case report* All others had died...

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# Infantile multisystem inflammatory disease: another case of a new syndrome

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**Abstract.** A 4-year-old girl with neonatal onset of chronic diffuse urticarial rash, head enlargement, protruding eye balls, bilateral arthritis of the knees, growth and mental retardation, and signs in blood and cerebrospinal fluid of chronic inflammation is presented and compared to two similar cases reported by us previously. Including this new patient there are now 14 documented cases with this specific inflammatory syndrome whose aetiology remains unknown.

In the present case, however, elevated antibody titres against I. ric. Borrelia antigen were found in the serum.

**Key words:** Infantile inflammatory disease – Neonatal onset

## Introduction

The description of two patients [9] identical to 11 cases reported in the literature since 1973 [6, 5, 1, 7, 2, 4] and an editor's proposal [3] that a new syndrome has emerged encourages me to describe another patient with features similar to those in two patients who were observed by us 11 years ago in Munich with an "infantile chronic relapsing inflammation of the brain, skin and joints".

## Case report

T.S. was admitted directly after delivery (birth date 03/18/81, gestation period 37 weeks, birth weight 2150 g, birth length 47 cm, head circumference 31 cm) to the Children's Hospital of the University of Giessen because of maculopapular skin rash, hepatosplenomegaly, anaemia and fever accompanied by recurrent infections (enteritis, bronchitis, rhinitis, cystopyelitis). One older brother of the patient is healthy and does not show any abnormalities. The father of the patient acquired a peculiar "rheumatic disease" with vasculitis (and uveitis?) in March 1979, 1 year prior to conception of the patient during a temporary stay in Argentina and was treated for several years. During the first hospital stay an X-ray of the patient's chest revealed hypertrophy of the heart. An ECG gave pathological results with a pronounced defect of depolarization. An EEG was normal. Chromosome analysis from peripheral blood lymphocytes was normal (46,XX). The amount of C-reactive protein was elevated. No circulating immune complexes were detected in the blood. Bone marrow aspiration showed increased granulopoesis (82.5%), decreased erythropoesis (1.5%) and normal lymphocytes (16%).

The further course was characterized by retarded growth and development, head enlargement with a wide open fontanel (cerebral atrophy could be demonstrated by CT scanning), protruding eye balls, conjunctivitis, blepharitis, massive enlargement of cervical, axillary and inguinal lymph nodes, bilateral arthritis of the knees and an itching maculo-papular rash which was aggravated in sun and heat. The recent appearance of the patient aged 4½ years including a knee X-ray is shown in Figs. 1a and b. Laboratory data from this and two previously described cases are summarized in Table 1. Treatment consisted of low dose pred-

Table 1. Synopsis of data from three patients with "infantile multisystem inflammatory disease"

| | U.B., born 1962 died 1974 | K.S., born 1973 died 1979 | T.S., born 1981 |
|---|---|---|---|
| *General* | | | |
| Sex | Female | Female | Female |
| Birth weight (g) | 3020 | 2020 | 2150 |
| Gestational age (weeks) | 38 | 34 | 37 |
| Growth | Below 10th percentile | Below 3rd percentile | Below 3rd percentile |
| Onset of symptoms | Since birth | Since birth | Since birth |
| *CNS* | | | |
| Intellectual development | Retarded | Retarded | Retarded |
| Perceptive deafness | Hearing aid (at 10 years) | ? | Since age 4 years |
| Head enlargement | + | + | ++ |
| Fontanelle (cm) | 3 × 3 (3 months); 1 × 1 (3 years) | 4 × 4 (8 months); 1 × 1 (16 months) | 6 × 4 (2 years); 4 × 3 (4 years) |
| Hemiplegia | rt (11 years) | ? | – |
| Chronic meningitis | Since age 4 years | Since age 4 months | Since age 4 months |
| CSF cells per µl | 1–1450 | 42–280 | 40–530 |
| Neutrophils (%) | 9–97 | 22–80 | 10–75 |
| Eosinophils (%) | 2 | 2 | 3–13 |
| CSF protein (mg/dl) | 25–165 | 30 | 44–561 |
| Brain biopsy | Diss. necrotiz. leukencephalopathy | Not done | Normal |
| *Eye* | | | |
| Protruding eye balls | + | – | + |
| Bilateral papilloedema | + | + | – |
| Uveitis | + | – | – |
| Blepharitis, conjunctivitis | – | – | + |
| Visual defect | At age 10 years | – | – |
| Strabismus | – | – | + |
| *Skin* | | | |
| Maculopapular rash | + | + | + |
| Pruritus | + | + | + |
| *Joints* | | | |
| Recurrent arthritis | Foot<br>Knees<br>Elbow<br>Wrists | Elbow<br>Knees | Knees |
| Abnormal X-ray picture | Swelling | Swelling, osteoporosis, metaphysal abnormality, irregular bone texture | Swelling, osteoporosis, metaphysal enlargement, epiphyseal enlargement, irregular bone texture |
| *Lymph nodes* | | | |
| Adenomegaly | + | + | ++ (axillary, inguinally) |
| *Liver-spleen* | | | |
| Hepatosplenomegaly | + | + | (+) |
| *Blood* | | | |
| Haemoglobin (g/dl) | 7.7–11.5 | 8.3–11.1 | 8.8–11.5 |
| Leukocytes per µl | 7600–21000 | 7200–26100 | 15700–38000 |
| Lymphocytes (%) | 7–66 | 17–55 | 5–21 |
| Sedimentation rate (1st h) | 27–85 | 17–55 | 65–87 |
| Serum iron (µg/dl) | 10–27 | 8–15 | 21 |
| Serum IgG (mg/dl) | 2120–3018 | 1250–1505 | 1087–1222 |
| IgA (mg/dl) | 293–404 | 63–238 | 234–382 |
| IgM (mg/dl) | 85–118 | 225–256 | 289–352 |
| Lymphotoxin/Interferon production | Not done | Not done | Impaired |

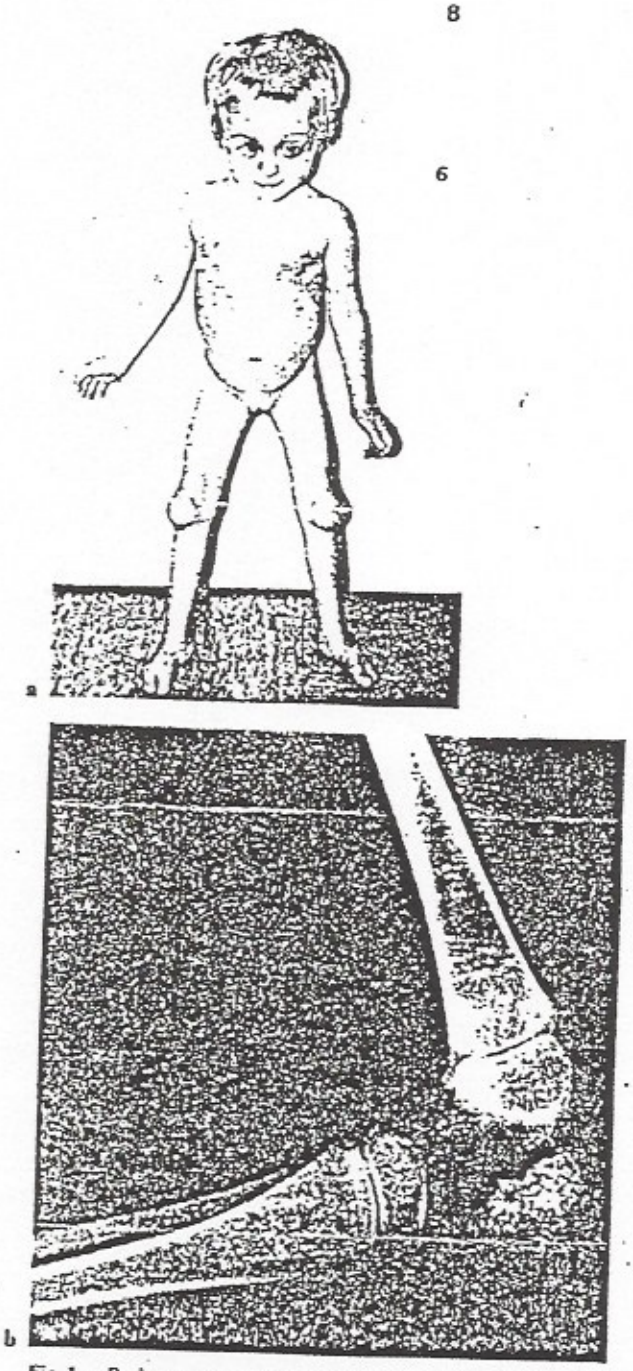

Fig. 1. a Patient aged 4¼ years (Photograph by Dr. J. Bauer, Gießen). b Radiograph of the right knee of patient T.S. aged 4½ years showing advanced punctate patellar ossification, enlarged epiphyses, periosteal reaction and widening of the femoral metaphyses. Marked osteoporosis is noted also. (Radiograph by Prof. Dr. W. Schuster, Gießen)

nisone (2.5–5 mg daily), which relieved the pruritis.

Examination of the blood lymphocytes at the ages of 6 months and 2 years revealed a partial T-cell defect with a diminished number of T-cells (114–1074 µl) and a weak response to the lectines PHA and ConA compared to controls. Production of lymphotoxin and interferon was impaired, i.e. there was a weak reaction to PHA and PWM, and no reaction to ConA (Prof. Dr. Rudolf Eife, Munich).

A lymph node biopsy (November 11, 1982) revealed acute lymphadenitis with particular lymph follicle hyperplasia and very little T-cell activation (Prof. Dr. A. Schulz, Giessen).

A skin biopsy (November 19, 1982) showed vasculitis, stroma oedema and marked eosinophilia (Prof. Dr. A. Schulz, Giessen).

A brain biopsy (August 18, 1983) – to rule out any subacute encephalopathy as this was seen in patient U.B. at autopsy – taken from the frontal lobe revealed no abnormality by light and electron microscopic examination (Prof. Dr. Peter W. Lampert, La Jolla/Calif.) This biopsy was done simultaneously with a ventriculo-peritoneal shunt operation to relieve any possible symptoms of increasing hydrocephalus.

At no time were viral or bacterial organisms isolated from blood, cerebrospinal fluid or biopsied tissues. All tests for Treponema pallida were negative.

## Discussion

The main findings of our three cases are summarized in Table 1. These findings are almost identical, indicating a chronic inflammatory process from birth involving many systems, but in particular the skin, the brain including the eyes, the joints with metaphyseal and epiphyseal abnormality and lymph nodes. Laboratory values are typical of chronic inflammation.

As pointed out by Yarom et al. [9] this new inflammatory syndrome should clearly be distinguished from juvenile rheumatoid arthritis. The prognosis of this disease is grave as two of our three patients have died at the ages of 12 and 6 years.

The neonatal onset suggests a prenatal infection. Though up to now no infectious particles have been detected in brain or in lymphatic tissue, even by electron microscopy, the search should go on; e.g. a tick-borne spirochetosis should always be looked for as maternal-fetal transmission of the Lyme disease Borrelia has been reported [8].

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**Note added in proof**

As suggested by Dr. J. Bauer, Children's University Hospital Gießen, serum and cerebrospinal fluid of patient, mother and father were examined for antibodies against Ixodes-ricinus-Borrelia (burgdorferi) antigen at the virus laboratory of Prof. Dr. R. Ackermann, Universitäts-Nervenklinik, Cologne: Elevated IgG titers (ELISA: 480, 370, 330 units) were found repeatedly in the patient's serum. The titres dropped (150, 160, 185 units) after 3 weeks of 9 Mega Penicillin G daily i.v. Titer's in the cerebrospinal fluid, however, were not elevated (1:2). The mother (asymptomatic) also had positive titres (ELISA: 290; 330 units), the father was negative (< 100).

The family has always lived in Hesse (near Giessen) near the large wooded areas (Marburg-Biedenkopf) where a 45 year old female with (B. Ixodes ricinus) Lyme disease was recently described (Goebel et al., Inn. Med. 12, 209, 1985). The patient was born in March (thus conceived and in early embryonic development the previous summer). Thus, it cannot be ruled out, that our patient developed this specific syndrome as a self-propagating inflammatory host response after an intrauterine infection with Lyme disease spirochaetes.