

MEDICAL GENETICS

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Cerebral complications in Schimke immuno-osseous dysplasia

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Abstract Schimke immuno-osseous dysplasia is a multisystem disorder consisting of spondylo-epiphyseal dysplasia, progressive renal insufficiency due to focal segmental glomerulosclerosis, and immunodeficiency. Cerebrovascular complications have only been described in five patients. Here we report a patient with prominent neurological symptoms most likely caused by transient ischaemic attacks.

Conclusion Neurological symptoms consisted of repeated brief spells of hemiparesis, motoric aphasia and diplopia. MRI studies of the CNS revealed progressive white matter lesions. Morphological changes as well as neurological deficits are compatible with cerebral ischaemia.

Key words Schimke immuno-osseous dysplasia · Spondylo-epiphyseal dysplasia · White-matter-lesions · Cerebrovascular complications

Abbreviations CBC complete blood cell count · PET positron emission tomography · TIA transient ischaemic attacks

Introduction

In 1974 Schimke et al. [8] described the combination of spondylo-epiphyseal dysplasia, progressive renal insuffi-

ciency and cellular immunodeficiency. In 1991 Spranger et al. [9], in a review of five cases, first suggested the term "Schimke immuno-osseous dysplasia" for this disease. The spectrum of clinical symptoms has further been defined by Ehrlich et al. [1], who were the first to describe neurological manifestations in this disease [2]. Schimke immuno-osseous dysplasia usually starts in early childhood and carries an unfavourable prognosis due to the complications of renal disease and immunodeficiency [3, 5].

We describe a 10-year-old boy with Schimke immuno-osseous dysplasia and white matter lesions of the central nervous system associated with recurrent transient ischaemic attacks (TIA).

Case report

Our patient was born in Bosnia in 1984 and first seen in 1993 because of a marked growth deficit. An older sister had died from chronic renal insufficiency of unknown origin at the age of 5 years. She was described as short. Photographs showed facial features of Schimke dysplasia. The patient was born as the second live child of non-consanguineous parents after a normal pregnancy with a weight of 2820 g and a length of 50 cm. The early childhood was unremarkable except for slow growth. Immunizations were performed without complications and there was no increased incidence of infections.

Physical examination of the 9-year-old patient showed a short trunked dwarfism with a height of 114 cm (<-3 SDS), an arm span of 115 cm and a sitting height of 59 cm (-4 SDS) (Fig. 1). Head circumference was 52 cm (50th percentile), the weight was 20.2 kg. Lumbar hyperlordosis was accentuated and multiple lentiginos were present on neck and trunk (Fig. 2). The hair was thin and the voice pitched. There was bilateral cryptorchism. The neurological examination was unremarkable.

Laboratory investigations showed persisting leukopenia with a minimal WBC of 1900/ml. T-cell subclasses revealed a deficit in CD4- and CD8-positive cells while RBC and platelets were normal. IgG was diminished (449 mg/dl), IgM (193 mg/dl) was elevated. IgA (158 mg/dl) was normal. C4-complement was 59 mg/dl (normal). A skin test with eight different antigens (Multi-Test Merieux) showed total absence of a cutaneous reaction. Tests for antinuclear antibody, anti-DNS antibody, antimitochondrial antibody, circulation immunocomplex as well as rheumatoid factor were negative. Clotting parameters (PT, PTT, fibrinogen, AT-III) were within

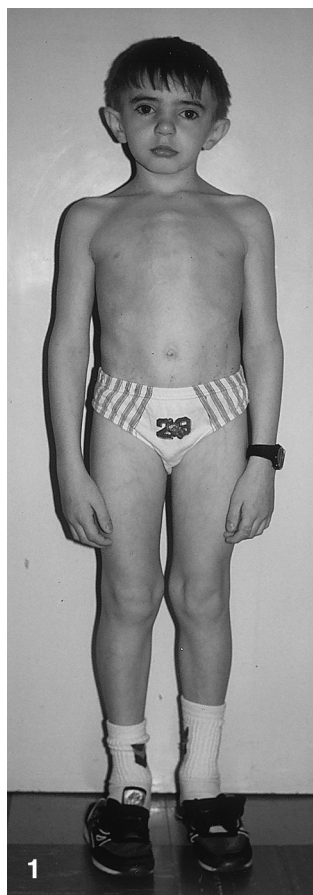
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Fig. 1 Clinical features of a 9-year-old boy with Schimke immuno-osseous dysplasia. Note triangular face with prominent tip of nose.

Fig. 2 Multiple characteristic lentigines on the trunk



normal limits. Total serum cholesterol was 364 mg/dl, LDL-cholesterol 222 mg/dl, HDL-cholesterol 68 mg/dl, with further progression of renal insufficiency, total serum cholesterol level reached a maximum of 968 mg/dl. Cerebrospinal fluid was normal as were screening tests for aminoacids, organic acids and mucopolysaccharidosis. Proteinuria and oedema were noted. Renal biopsy showed focal segmental hyalinosis and a slight increase in mesangial cells with sclerosis. There was no evidence of microthrombi, the tubules were atrophic. Immunohistology showed segmental deposits of IgM complement (C1, C3, C4).

Radiographs showed spondylo-epiphyseal dysplasia. Duplex-Doppler-sonography of the cerebral vessels and echocardiography were unremarkable. Repeated EEG showed unspecific changes and left hypersynchronous activity parieto-temporal on one occasion. Visually evoked potentials were within normal limits.

Repeated MRI showed progressive focal hyperintensities in the periventricular and frontal white matter with wedge-shaped extension to the cortex. In the T2 image, lesions with a diameter of 1 cm were partially confluent. There was no enhancement after i.v. contrast medium was given. The white matter lesions were interpreted as postischaemic gliosis due to recurrent ischaemic and/or embolic episodes (Fig. 3a-c). The MRI in February 1995 showed no further progression of these lesions with partial remission of smaller lesions. Positron emission tomography (PET) with flumazenil for imaging of the benzodiazepine receptor concentration showed a circumscribed perfusion defect on the right temporo-parieto-occipital region with a diminished benzodiazepine receptor density in this region.

Cyclosporin A was given for a period of 9 months but had no effect on proteinuria. In spite of therapeutic efforts including diuretics, ACE inhibitors and lipid-lowering agents the patient developed progressive renal insufficiency and severe hypertension with peak blood pressures up to 220/150 mmHg which became

increasingly resistant to therapy with dihydralazin, metoprolol, diltiazem and enalapril. Maintenance haemodialysis had to be started in July 1994.

At the age of 10 years the child first complained of paresthesia in the right hand and motoric aphasia lasting a few minutes. The patient also complained of periods of diplopia. Similar symptoms recurred three times during the next 4 months both on the right and the left side unresponsive to pentoxifyllin and aminoacids. Symptoms were unrelated to high blood pressure peaks.

Discussion

Neurological symptoms have previously been described in patients with Schimke dysplasia as TIA in five patients [2], comprising headaches, visual disturbances, motoric aphasias, and hemiparesis; one child subsequently died from a stroke episode. In three patients PET showed a disturbed perfusion in cerebral and cerebellar arteries [2]. In contrast, CT and MRI performed in two of these patients failed to demonstrate morphological changes of the CNS. In our patient, the term "TIA" was used to describe the clinical phenomenon of recurrent, short-term and completely reversible neurological deficits. Nevertheless they were ascribed to white matter lesions on repeated MRI studies as well as perfusion deficits on PET scanning indicating persistent focal ischaemia. The exact pathomechanism of TIA is not known, but they are closely related to vascular

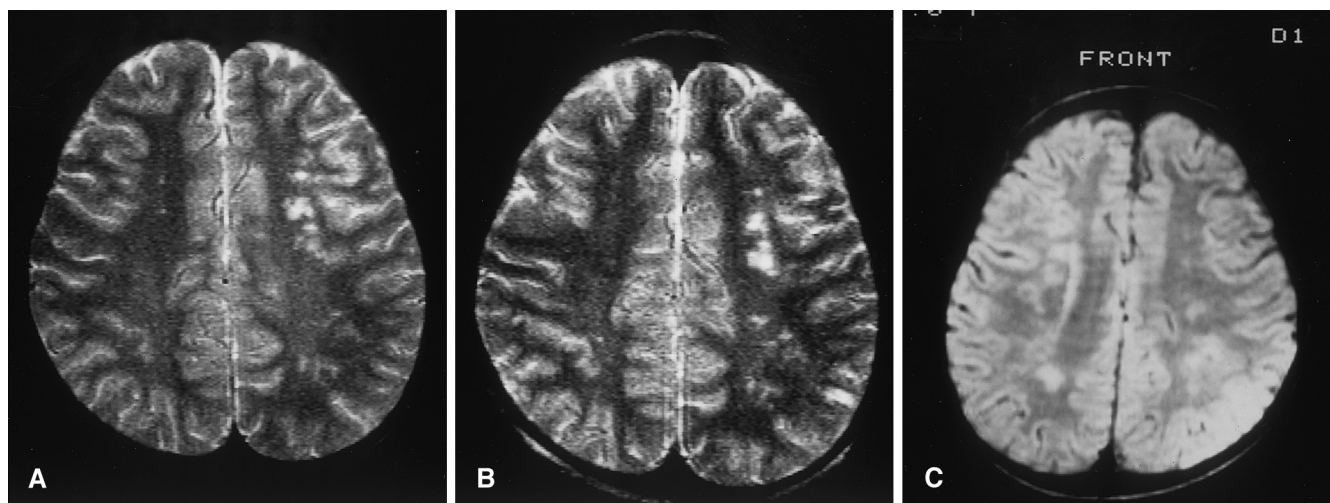


Fig. 3 Sequence of MRI of the CNS. (A) April 1994: focal white matter lesions with multiple prominent spots lined up next to the left cortex, which is partly affected. Smaller lesions can be found in the parieto-occipital region on both sides. (B) May 1994: progression of the hyperintensities in number and size, especially pronounced in the left parieto-occipital region. (C) September 1994: formerly scattered spots of the left parieto-occipital region are now confluent. The cortex next to the lesion is affected as well. Additional lesions are found within the right-sided white matter. Part remission of the frontal defects

stenosis and ulceration due to atherosclerosis and thrombus formation in the majority of cases. On autopsy two children with immuno-osseous dysplasia had extensive atherosclerosis of all major arteries including the carotid arteries and the coronary arteries [9]. With pronounced hyperlipidaemia and arterial hypertension being risk factors [4, 6] atherosclerotic lesions are the most likely explanation for the neurological symptoms. Neither cardiac emboli nor antithrombin-III deficiency were found. Finally, immune vasculitis could be discussed as a possible cause of the neurological deficits; however, the muscle biopsy of one patient and the autopsy of three other patients showed no vascular changes compatible with vasculitis [7, 9]. The therapy of cerebral complications is empirical. If symptoms are due to generalized cerebral vascular disease, frequency and intensity of the neurological deficits are likely to increase regardless of a recommended therapy with pentoxifyllin and aminoacids. We suggest that extensive radiological examination including MRI is indicated early in the course of the disease.

Annotation The patient reported above was presented at the fourth symposium on Paediatric Neurology "The unsolved case" in Göttingen.

References

1. Ehrich JHH, Offner G, Schirg E, Hoyer PF, Helmchen U, Brodehl J (1990) Association of spondylo-epiphyseal dysplasia with nephrotic syndrome. *Pediatr Nephrol* 4:117–121
2. Ehrich JHH, Burchert W, Schirg E, Krull F, Offner G, Hoyer PF, Brodehl J (1995) Steroid resistant nephrotic syndrome associated with spondyloepiphyseal dysplasia; transient ischemic attacks and lymphopenia. *Clin Nephrol* 43, 2:89–95
3. Gilchrist DM, Harley FL (1992) Schimke immuno-osseous dysplasia. *J Pediatr* 120:497
4. Hauser RA, Lacey M, Knight MR (1988) Hypertensive encephalopathy: magnetic resonance imaging; demonstration of reversible cortical white matter lesions. *Arch Neurol* 45:1078–1083
5. Ludman MD, Cole DEC, Crocker JFS, Cohen MM (1993) Schimke immuno-osseous dysplasia: case report and review. *Am J Med Gen* 47:793–796
6. Querfeld U (1995) Störungen des Lipoproteinstoffwechsels bei Kindern mit chronischen Nierenerkrankungen *Monatsschr Kinderheilkd* 143:232–239
7. Santava A, Zapletova J, Michalkova K, Hanakowa S, Kopriva F, Santavy J, Dusek J, Kleinova D (1994) Spondyloepiphyseal dysplasia with nephrotic syndrome (Schimke immuno-osseous dysplasia). *Am J Med Gen* 49:270–273
8. Schimke RN, Horton WA, King CR, Martin NL (1974) Chondroitin-6-sulfate mucopolysaccharidosis in conjunction with lymphopenia, defective cellular immunity and nephrotic syndrome. *Birth Defects* 10:258–266
9. Spranger J, Hinkel GK, Stöss H, Thoenes W, Wargowski D, Zepp F (1991) Schimke immuno-osseous dysplasia: a newly recognized multisystem disease. *J Pediatr* 119:64–72