Chronic juvenile toxic epidemic syndrome

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SUMMARY The clinical manifestations in 21 children with chronic toxic epidemic syndrome (TES) and musculoskeletal manifestations were analysed and compared with those of the adult population. The sex ratio (2.5:1, F/M) was different from the one found in adults (6:1, F/M). The neuromuscular syndrome, the scleroderma-like picture, the pulmonary hypertension, and the Raynaud's phenomenon characteristic of TES were similar to those in adults but milder in children. The less severe vascular endothelial lesions found on microscopic examination might explain the better prognosis in this age group.

Key words: arthralgias and arthritis, scleroderma-like, non-necrotising vasculitis, toxic peripheral neuropathy, osteopenia.

The toxic epidemic syndrome (TES) was described in Spain in May 1981. It followed the consumption of adulterated rapeseed oil. The disease evolved through three phases: (1) acute, with rashes, pleuro-pulmonary manifestations, and eosinophilia; (2) intermediate, with severe muscular pains and thromboembolic lesions; and (3) chronic, with an overlapping of a neuromuscular syndrome, scleroderma-like involvement, Raynaud's phenomenon, and pulmonary hypertension.¹ Nearly 15% of the patients progressed to the chronic stage of the disease.

The typical pathological finding was a non-necrotising vasculitis and an increase in fibrous tissue at various levels.²

The clinical and pathological features of this syndrome have been reported in Spanish and British publications in the last few years.^{1–6} The musculoskeletal symptoms of TES in adults have been analysed and the results will be published elsewhere. The present report, based on a study of our hospitalised patients, describes the musculoskeletal manifestations in children and compares them with those in adult population.

Patients and methods

Patients aged 14 or less, diagnosed as suffering from TES according to previous criteria, and having musculoskeletal manifestations, were studied in our special TES paediatric unit.⁷ The children were examined by one of the authors and their charts reviewed. Occasionally, missing data were obtained retrospectively. We looked particularly for the presence of musculoskeletal manifestations. The patient's weight on examination was compared with the weight at the beginning of the disease. Mild, moderate, or severe malnutrition was diagnosed when the difference between these values was 10, 15, or >15% respectively.

The diagnosis of scleroderma-like disease, Raynaud's phenomena, and pulmonary hypertension was made clinically. The diagnosis of neuromuscular syndrome was made according to previously published criteria.⁵ A blood sample was obtained from each patient by the same procedure as that used in the follow-up controls of these patients.

Laboratory investigations. Full blood counts, sedimentation rate, and tests for C-reactive protein (Difco Laboratories, Detroit, Michigan, USA) and rheumatoid factor (Hyland Diagnostics, Deerfield, Illinois, USA) were carried out by standard tech-

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niques. ANA and anti-DNA were detected by immunofluorescence with mouse liver and *Chritidia lucillae* as substrates. The presence of anti-ENA (extractable nuclear antigen) was determined by double immunodiffusion in agar against rabbit thymus extract (Pel-Freeze, Biologicals, Rogers, AK, USA), and sera with known anti-Sm, anti-RNP, and anti-SSB specificity were used as references. C3 and C4 were determined by radial immunodiffusion (Behring Institute, Behringwerke AG, Marburg, Germany).

Radiography. Hand and foot radiographs from 18 patients were available for review. In addition symptomatically affected joints were examined.

Pathology. Deep skin biopsies taken from upper back (1), thigh (1), anterior abdomen wall (1), and shoulders (9) were stained with haematoxylin-eosin.

Results

Twenty-one out of 75 children with chronic TES had musculoskeletal signs or symptoms and were included in the study. No differences in the mean age or sex between children with or without musculoskeletal manifestations were observed. The youngest child was 5 years old (Table 1). The sex ratio (2.5:1, F/M) was different from that found in the chronic phase of the adult population (6:1, F/M).

The date of diagnosis of the disease, the interval between this date and the beginning of musculoskeletal manifestations, and the treatment previous to the study were similar in both children and adults (Table 1). Twelve children were treated with more than 7.5 mg daily of prednisone for more than three weeks; six received 4 mg daily of superoxide dismutase (Peroxinorm, Andromaco, Spain, or Ontosein, Zambelletti, Italy) for two weeks, fol-

lowed by 4 mg every other day for three months, then 4 mg twice a week for a further nine months. Three were treated with 60 mg daily of D-penicillamine.

In the acute phase the most common picture was fever with exanthem (Fig. 1), which in 14 patients appeared with pleuropulmonary involvement and in five with pleuropulmonary involvement and abdominal pain. Isolated fever or arthralgias were found in only one patient. The incidence of other clinical manifestations was similar to that found in all the children hospitalised (Table 2).

Subjective complaints such as malaise (30% children vs. 80% adults), dyspnoea (29% vs. 66%), myalgias (41% vs. 80%) and chest pain (12% vs. 39%) were noted less frequently in children than adults.

In the chronic phase arthralgias were found in all 21 patients. They were symmetrical in 18 and

Fig. 1 Clinical pictures in the acute phase in 21 children with musculoskeletal manifestations.

Table 1 Characteristics of children and adults with chronic TES who had musculoskeletal lesions

	Children (n=21)	Adults (n=50)
Age (years)	10.7 (5 to 14)	31.8±15.7 (15 to 72)
Sex ratio F/M	2.5/1	6/1
Date of TES diagnosis	May 15±15 days	May 15±15 days
Interval to joint complaints (months)	1.9 (0 to 5)	1.7 (0 to 4.5)
Corticosteroid treatment (patients)	13	22
SOD* treatment (patients)	6	11

* Superoxide dismutase. ±=Standard deviation.

Table 2 Clinical manifestations among 125 hospitalised children with TES between May and June 1981

	n	%
Fever	91	73
Exanthem	80	64
Pruritus	66	53
Myalgias	51	41
Cough	42	34
Malaise	37	30
Dyspnoea	36	29
Abdominal pain	34	27
Headache	28	22
Anorexia	24	19
Oedema	19	15
Chest pain	16	12
Arthralgias	10	8
Dysphagia	4	3

affected elbows, knees, hands, and wrists in this order (Table 3). This type of pain was always caused by movement. Arthritis was seen in two patients, in one in both knees and in the other in the wrist (Table 3). Other joint related symptoms were similar to those of the adults, but the typical upper limb deformity, reduced distance between the lips on maximal mouth opening, and morning stiffness were not as frequent (Tables 4 and 5).

The overall clinical picture (Table 4) was milder in children than adults. However, the incidence of flexion-contracture was high (Table 4). The presence of scleroderma-like, neuromuscular syndrome, and pulmonary hypertension was common (Table 4). The neuromuscular syndrome was milder in children (Table 6), judged by previous criteria.⁵ Generalised or localised muscle atrophy was seldom present.

Table 3 Joint manifestations in children and adults with chronic TES

	Arthralgias %		Arthritis %	
	Children (n=21)	Adults (n=50)*	Children (n=21)	Adults (n=50)*
Elbow	86	94	—	2
Knee	86	90	5	8
PIP	62	60	—	—
Wrist	57	84	5	—
MCP	57	74	—	2
Ankle	43	72	—	4
Shoulder	38	40	—	—
DIP	29	26	—	—

* TES: Musculoskeletal manifestations. Mateo *et al.*¹⁴

Table 4 Clinical manifestations in chronic TES in children and adults

Musculoskeletal	Children n=21 (%)	Adults n=50 (%)*
Arthralgias	21 (100)	50 (100)
Flexion-contractures	11 (52)	33 (66)
Palm retraction	9 (43)	43 (86)
Abnormal maximal oral aperture	6 (28)	37 (74)
Morning stiffness	5 (24)	41 (82)
Articular crepitus	3 (14)	14 (28)
Arthritis	2 (9)	6 (12)
Extra articular		
Scleroderma-like	20 (95)	46 (92)
Neuromuscular syndrome	20 (95)	44 (88)
Raynaud's disease	5 (24)	24 (48)
Pulmonary hypertension	3 (14)	11 (22)

* See Mateo *et al.*¹⁴

Table 5 Distribution of severe articular functional limitation among children and adults with chronic TES

	Children n=21 (%)	Adults n=50 (%)*
Wrist	7 (41)	19 (38)
Ankle	5 (23)	32 (64)
Knee	3 (14)	5 (10)
Elbow	1 (5)	1 (2)
Hip	1 (5)	10 (20)
Shoulder	1 (5)	3 (6)

* See Mateo *et al.*¹⁴

Table 6 Neuromuscular syndrome in chronic TES in children and adults*

	Children n=21 (%)	Adults n=50* (%)
Nil	1 (5)	—
Mild	13 (62)	9 (18)
Moderate	4 (19)	13 (26)
Severe	3 (14)	22 (44)

* See Portera *et al.*⁵

† See Mateo *et al.*¹⁴

The scleroderma-like distal involvement was frequent in children than adults (35% vs. 60%), but no difference was found in the proximal areas. Skin infiltration (Fig. 2) and skin atrophy were observed at the same time in patients. Localised forms of infiltration with a linear distribution were present in three patients (Fig. 3). Pulmonary hypertension was asymptomatic and detected only on physical examination. Raynaud's phenomenon occurred in 25% of patients.

The blood count, sedimentation rate, and complement levels were normal. Tests for C-reactive protein and latex rheumatoid factor were negative. In 15 out of the 17 patients tested the ANA test was positive. In four of them the titre was > 1:40, and in the remaining 11 it was between 1:10 and 1:40. Anti-DNA and anti-ENA antibodies were never detected.

Radiographs showed diffuse and juxta-articular osteopenia in the hands and feet of 16 out of the 18 patients examined. Other types of osteopenia found in adults (subchondral, speckled, and metaphyseal band distribution) were absent. Narrowing of joint space, erosions, and capsular or soft tissue calcifications were not observed. The skin biopsies showed (Fig. 4) a marked increase in fibrous tissue, with destruction of appendages extending deep in the hypodermis. No lesions were seen in the small or medium size blood vessels.

Fig. 2 Hands of a child with TES showing skin infiltration.

Fig. 3 The arm of a child with TES shows a localised form of infiltration with a band distribution.

Discussion

The TES outbreak affected 17 391 patients, of whom 3210 were children aged below 14.⁸ Overall 15% of the affected population progressed to the chronic disease. In our hospital we saw 717 adults and 125 children, 15% of the adults and 60% of the children (75 patients) progressed to the chronic phase. This higher incidence of chronic disease in the children may be a result of their having been hospitalised because they had a more severe form of the disease.

Our study was based on the analysis of 21 selected children with chronic TES seen in our hospital. The mean age, sex ratio, and clinical symptoms were

similar to those in the other children with the chronic stage of the disease but without musculo-skeletal manifestations. The incidence of musculo-skeletal manifestations (28%) was lower than in adults. Arthralgias, very common in adults, were probably underestimated in children.

In previous reports we suggested that in adults the female sex was one of the determinants for chronic disease. In children the sex difference in the chronic phase was minimal. A difference in sex ratio between children and adults in rheumatic diseases is well known.⁹ The chronic phase of TES is similar to some rheumatic diseases.¹ Generally the sex ratio in TES parallels that in some rheumatic diseases.

In patients with scleroderma-like disease induced

Fig. 4 Skin biopsy showing an increase in fibrous tissue extending deep in the hypodermis. The appendages are destroyed. (Haematoxylin and eosin, $\times 40$).

by vinyl chloride the HLA-DR3 haplotype has been found in a high frequency, but not in those exposed to the toxin who did not develop the chronic disease.¹⁰ A study of HLA-DR haplotypes in our population is being undertaken, but a preliminary report from another hospital¹¹ supports the theory that susceptibility to the development of a chronic disease in patients exposed to the toxic oil may be genetically determined.

In children the musculoskeletal manifestations were similar to those of adults but less frequent and milder. The lower incidence of Raynaud's phenomena and distal involvement may represent a lesser severity of distal vascular lesions.

Other extra-articular manifestations were also similar and less severe. The linear distribution of scleroderma was typical in children but never found in adults. The milder neuromuscular syndrome and absence of symptomatic pulmonary hypertension may be related to a less severe involvement of vascular structures.

In TES the functional disability depends on skin, neuromuscular, and joint involvement. In children lesions of these organs were less severe, and this would explain the better functional capacity of this subpopulation of patients.

The height of affected children could not be

exactly measured because of the contractures. The incidence of weight abnormalities was comparable with those of any other chronic disease affecting children.¹²

No specific laboratory abnormalities were detected. Indicators of acute inflammation were absent. The ANA test was positive as in adults. Antihistone antibodies produced by ingestion of chemicals of the aromatic amines and hydrazine class have been already reported. The toxic oil was denatured with some aromatic amines.¹³ These types of antibodies are under investigation in our patients.

The radiographs of our children showed some differences from adults. The typical reported forms of osteopenia (speckled, metaphyseal bands) were not found. The relationship between these types of osteopenia and vascular structures has been previously mentioned,¹⁴ and, as the vascular damage is probably less severe in children than adults, this would account for the milder clinical and radiological manifestations.

The skin biopsies revealed a marked increase in fibrous tissue. Vascular lesions, commonly seen in adults, were not present. This finding could be a sampling error. However, most of the biopsies were taken proximally, and both children and adults have a similar degree of involvement at this level. Possibly therefore children recover faster from lesions or have minimal endothelial damage. Epidemiological investigations have found a relationship between the severity of the disease and the amount of oil consumed among the affected and unaffected relatives.¹⁵ It is possible that children generally consumed lesser quantities. Other factors related to sex and genetic susceptibility cannot be excluded.

In conclusion, the clinical, laboratory, radiographic, and pathological manifestations of TES in children are similar to those in adults but milder in intensity. In TES most of the manifestations could be explained on the basis of the generalised vascular lesion. Whether the milder syndrome seen in children represents a milder endothelial lesion related somehow to the absence of female sex hormones, the amount of toxic oil ingested, and genetic factors remains a matter for debate.

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