Childhood macrophagic myofasciitis—consanguinity and clinicopathological features

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Received 24 July 2003; received in revised form 16 December 2003; accepted 22 December 2003

Abstract

Macrophagic myofasciitis has been almost exclusively detected in adults only. We describe six children of Arab Moslem origin with this disorder. Three presented with hypotonia, developmental delay and seizures and were evaluated for a mitochondrial disorder. The other three children had hypotonia and predominantly motor delay. Five of the six families were consanguineous. A massive collection of macrophages was present in the fascia and adjacent epimysium in all biopsies. The macrophages were periodic-acid-Schiff positive and immunoreactive for CD68. One biopsy which was evaluated by electron microscopy and energy-dispersive X-ray microanalysis showed crystalline structures containing aluminum in macrophages. Two children with motor delay and hypotonia were treated with oral prednisone for 3 months with no clinical improvement. Genetic predisposition probably accounts for the variability in the prevalence of macrophagic myofasciitis in different populations. At least in childhood, there seems to be no connection between macrophagic myofasciitis as a pathological entity and the clinical symptoms and signs.

Keywords: Macrophagic myofasciitis; Immunizations; Muscle biopsy; Children

1. Introduction

The recent development of new effective vaccines and the broadening of vaccination programs nurture the expectation of enhancing public health by eliminating common infectious diseases [1]. However, even though immunizations have an extraordinary safety record overall, the wide distribution of new vaccinations has raised concern over additional new side effects [2].

A new clinical–pathological entity, macrophagic myofasciitis, was initially and mainly reported in France [3]. Subsequently, fewer cases have been described in other parts of the world, including Spain, Germany and the USA [4–6]. The clinical features of these adult patients varied. Most patients underwent biopsy due to myalgia, arthralgia, muscle weakness, asthenia or fever with the presumptive diagnosis of polymyositis or polymyalgia rheumatica [3]. In isolated cases, macrophagic myofasciitis was associated with renal fibromuscular dysplasia [7] or inclusion body myositis [8], and a few patients had an associated demyelinating central nervous system disorder [9]. Muscle pathology in all these cases was characterized by a pattern of infiltration of the epimysium, perimysium and perifascicular endomysium by periodic-acid-Schiff (PAS) positive cells of the macrophage lineage.

It has been recently shown that macrophagic myofasciitis represents an unusual local reaction to intramuscular
injections of aluminum-containing vaccines [6,10]. Interestingly, although the majority of vaccinations are administered during infancy and early childhood, only a few children with this disorder have been described in the literature [4,6]. We present the clinical features and muscle pathology of six infants and young children with macrophagic myofasciitis. Five of the six families were consanguineous. The possible relationship between muscle pathology, aluminum in vaccinations, consanguinity and the clinical findings in this unusual disorder is discussed.

2. Methods

2.1. Patients: case reports

2.1.1. Patient 1
This 3-year-old boy was a product of a normal pregnancy and a cesarean delivery due to suspected overweight. His birth weight was 3900 g. He was the only child of first-degree cousins of Arab Moslem origin. Three children in the father’s family had died from an undiagnosed disease in infancy. At 4 months of age, he was evaluated for accelerated head growth and general hypotonia (Table 1). Magnetic resonance imaging studies of the brain revealed enlarged lateral ventricles and a few hyperintense areas in the white matter of the cerebral hemispheres on T2 sequence. Lysosomal enzyme studies for Krabbe and metachromatic leukodystrophy were negative. The levels of serum and cerebrospinal fluid lactate, urine organic acids, serum amino acids, creatinine kinase, vitamin B12, very long chain fatty acids and phytanic acid were all within normal limits.

At the age of 3 years and 4 months, his head circumference was in the 50th percentile. The child demonstrated marked psychomotor delay: he never crawled or sat, had no fear of strangers and spoke only a few words. Neurological examination revealed intact cranial nerves. There was generalized severe hypotonia and weakness, with normal deep tendon reflexes. In view of the profound developmental delay and the abnormal magnetic resonance imaging findings in the context of a contributory family history, mitochondrial encephalomyelopathy was considered and a quadriceps muscle biopsy was performed at that age.

2.1.2. Patient 2
This child was evaluated at age 20 months due to hypotonia, motor delay and elevated serum creatine kinase. She was the product of an uneventful pregnancy and delivery and her birth weight was 3500 g. Her parents were second cousins of Arab Moslem descent. Five male siblings were healthy and there was no history of any neuromuscular diseases in the family. At 7 months of age, she was first noticed to have hypotonia and motor delay. She sat independently at 1 year of age and started walking at 19 months. On examination (age 20 months), the child was alert and had normal social interaction. Her head circumference was 46 cm (15th centile). All cranial nerves were intact. Appendicular and axial tones were decreased and her deep tendon reflexes were reduced throughout. She also had bilateral hypertrophy of the calves.

At age 3 years, the child had proximal weakness of the lower extremities and a waddling gait. She experienced difficulty in climbing stairs and rose from the floor by performing the Gower’s maneuver.

The values for serum creatine kinase were increased; 782–1250 IU/l (N 0–170). Serum lactate and carnitine as well as urine for amino acids, organic acids and reducing substances were normal. A computerized tomography scan of the brain was normal as were lower limb nerve conduction studies. The electromyography was normal, except for some fibrillation potentials and low amplitude polyphasic units in one area of the right vastus medialis. An open biopsy of the left quadriceps muscle was performed at 2 years of age. The child was treated for 3 months with prednisone 2 mg/kg without any apparent benefit.

2.1.3. Patient 3
This 3-year-old girl presented with global developmental delay and seizures. She was a product of a normal pregnancy and delivery. Her birth weight was 3500 g.

<table>
<thead>
<tr>
<th>Patient</th>
<th>M/F</th>
<th>Age at biopsy (months)</th>
<th>Consanguinity of parents</th>
<th>Family history</th>
<th>Presenting symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>40</td>
<td>First cousins</td>
<td>Three cousins died in infancy</td>
<td>Global developmental delay</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>20</td>
<td>Second cousins</td>
<td>Negative</td>
<td>Hypotonia, elevated serum CK</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>36</td>
<td>No</td>
<td>Negative</td>
<td>West syndrome, global developmental delay</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>20</td>
<td>First cousins</td>
<td>Cousin (patient 5), second cousin died age 13 months</td>
<td>Hypotonia, failure to thrive</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>22</td>
<td>First cousin</td>
<td>Cousin (patient 4)</td>
<td>Hypotonia, failure to thrive</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>4</td>
<td>First cousins</td>
<td>Sibling with hypotonia, microcephaly, seizures</td>
<td>Hypotonia, developmental delay</td>
</tr>
</tbody>
</table>
The parents were non-consanguineous Arab Moslems. There were two unaffected siblings and no history of neurological or neuromuscular diseases in the family. The child developed normally during the first year of life. She spoke a few words at the age of 1 year but never acquired additional words thereafter. She walked independently at 17 months of age. At age 18 months, she had myoclonic jerks and head drop episodes as well as severe restlessness. Repeated electroencephalograms showed general epileptic activity of poly-spike and wave, and burst suppression was noted in some studies. Her clinical diagnosis was defined as progressive myoclonic epilepsy and she was treated with various antiepileptic medications including vigabatrin, valproate, clonazepam, clobazam, lamotrigine, topiramate and adrenocorticotropic hormone.

On examination at age 2 years and 4 months, her head circumference was 46.5 cm (5th centile). The child showed interest in the environment but she was not heard to speak. All cranial nerves were intact and there were no cerebellar signs or significant sensory deficits. Her muscle tone and strength were normal. Motor function was normal and she walked, ran and jumped according to her age level. Her deep tendon reflexes were normal throughout.

Evaluation included normal magnetic resonance images of the brain. Serum ammonia, carnitine, amino acids, very long chain fatty acids and urine organic acids, as well as lysosomal enzymes for metachromatic leukodystrophy, Krabbe, GM1 gangliosidosis and Tay-Sachs were normal. A quadriceps muscle biopsy at age 3 years revealed normal activity of the muscle respiratory chain complexes, however, there was decreased pyruvate oxidation on polarography (56% of citrate synthase activity) which suggested mitochondrial assembly or maintenance defect. Glutamate, pyruvate and ascorbate oxidation on polarography were normal as was pyruvate dehydrogenase activity.

2.1.4. Patient 4

At 2 months of age, this female infant presented with hypotonia and head lag as well as failure to thrive, with her weight, height and head circumference under the 5th percentile. Her birth weight was 3120 g and the perinatal period was normal. The parents were first cousins of Arab Moslem origin. Her one male sibling was healthy. One son of the mother’s cousin died at age 13 months of unknown causes and she is the cousin of patient 5.

On examination at age 7 months, she demonstrated adequate social interaction. Her cranial nerves were intact. There was no ptosis or ophthalmoplegia. She exhibited significant head lag and severe limb and axial hypotonia with predominantly proximal weakness. Her deep tendon reflexes were normal in the upper extremities and absent in the lower extremities. There were no contractures. Spontaneous movements were minimal. At age 20 months, she had severe muscle weakness and hypotonia with head lag and lay in a frog position. She was unable to sit independently. Cognitively she could speak a few words, clap her hands and respond to simple commands.

Laboratory investigations revealed normal serum creatine kinase, glucose, liver and renal function tests. Urine tests for reducing substances, amino acids, organic acids and plasma amino acids were within normal limits. Genetic analysis failed to detect deletion of the SMN and NAIP genes. Respiratory chain complex activity was normal in a quadriceps muscle biopsy performed at 7 months of age. Treatment with prednisone 2 mg/kg for 3 months failed to result in any improvement in muscle strength.

2.1.5. Patient 5

This female infant is a second cousin of patient 4. She was born after 30 weeks of gestations following amnionitis. Birth weight was 1200 g. The mother reported decreased fetal movement a few weeks prior to delivery. Apgar scores were 6 and 8 at 1 and 5 min, respectively, and perinatal complications included respiratory distress syndrome that required ventilation for 3 days and a group B beta hemolytic Streptococcus sepsis. The parents were first cousins of Arab Moslem descent. The other four siblings were healthy. She was referred to our clinic at the age of 11 months with hypotonia, psychomotor delay and failure to thrive. Past history was positive for several episodes of pneumonia. On examination weight was 5400 g and head circumference 39 cm (both under 3rd percentile). The infant was alert and responsive but no spontaneous vocal sounds were heard. She was extremely hypotonic with head lag and was very weak with difficulty in spontaneous movements. She was unable to turn from prone to supine or raise her head and chest in the prone position. Deep tendon reflexes were obtained only in the upper extremities. Brain ultrasound and ophthalmologic evaluation were normal. Nerve conduction studies of the right ulnar and median and tibial and peroneal motor nerves as well as bilateral sural sensory nerves were normal except for absence of F waves throughout. The electromyography of bilateral tibialis anterior muscles bilaterally revealed complex repetitive discharges, large motor unit potentials and decreased recruitment. A metabolic screen including serum lactate, ammonia, carnitine, serum amino acids and urine organic acids was normal. Brain magnetic resonance imaging showed mild enlargement of all cerebral spinal fluid spaces.

2.1.6. Patient 6

A 4-month-old male infant was born at term after an uneventful pregnancy and delivery. The parents were first cousins of Arab Moslem descent. Their first child had died at age 6 months with seizures, microcephaly, hypotonia and developmental delay. Hypotonia and developmental delay were first noted in our patient at the age of 2 months. In addition, he had a rash of unknown etiology on his four extremities and buttocks and left uretero-pelvic junction stenosis. At 4 months of age, he was admitted to an intensive care unit with right lung atelectasis due to aspiration...
pneumonia and status epilepticus. On admission, he was stuporous and responded only to painful stimuli. His head circumference was 42 cm. The pupils were equal and reacted to light. He had severe head lag and generalized symmetric hypotonia as he lay in a frog position, his deep tendon reflexes were normal. He was ventilated and there was initial improvement in his respiratory function. However, atelectasis of both lungs recurred and this was followed by respiratory deterioration and cardiac arrest. He died on his 11th day of admission. Laboratory evaluation had included normal thyroid function tests and normal serum creatine kinase, ammonia and quantitative amino acids analysis. Serum and CSF lactate levels were normal. Computerized tomography and magnetic resonance imaging of the brain demonstrated cerebellar hypoplasia and mild dilatation of the lateral ventricles. An open quadriceps muscle biopsy was performed to evaluate the possibility of a mitochondrial disease. It revealed normal activity of the muscle mitochondrial respiratory chain enzymes.

2.2. Vaccination history

The vaccination history of five children prior to muscle biopsy is summarized in Table 2. Patient 6 died at the age of 4 months and his history is unavailable.

2.3. Light microscopy

A quadriceps muscle biopsy from each case was prepared for paraffin sections, histochemical stains and electron microscopy (EM). Histochemistry performed on frozen sections included hematoxylin and eosin, modified Gomori trichrome, ATPase reaction following alkaline (pH 9.4) and acidic (pH 4.3) preincubation, nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR), succinate dehydrogenase, cytochrome c oxidase, PAS, PAS following prior diastase digestion and acid phosphatase. Sections were screened with monoclonal antibodies to dystrophin (Ncl dys 1,2,3), alpha sarcoglycan (Adhalin) (Ncl-a-sarc) and Laminin alpha 2 chain (merosin), Novocastra (Newcastle upon Tyne, UK) and stained with CD68, CD1A, leukocyte common antigen (LCA, Dako, Copenhagen, Denmark), CD3, and CD20 (Zymed, San Francisco, USA). Stains for microorganisms included the Brown and Brenn stain, Ziehl-Nielsen and Gomori silver methenamine.

2.4. Electron microscopy

For the EM examination, small portions of biopsied muscle specimens were fixed in 2.5% glutaraldehyde solution. The stained (uranyl acetate–lead citrate) sections were observed by a Tecnai 12-transmission EM operated at 120 kV (Philips or Jeol 100-CX). Electron micrographs were taken at nominal magnifications of 2500–28 000 × using a MegaView II CCD camera (SIS, Munster, Germany).

2.5. Energy-dispersive X-ray microanalysis

Energy-dispersive X-ray microanalysis measurements were carried out from unstained sections by an EDAX Si(Li) detector with an ultra-thin window and energy resolution of 137 eV, mounted on a CM120 transmission EM (fei-Philip Eindhoven, Holland) operated at 120 kV.

3. Results

3.1. Muscle pathology

The histopathological features were almost identical in all six cases. There was a massive collection of medium- to large-sized macrophages with abundant basophilic finely granular cytoplasm in the muscle fascia and adjacent epimysium (Fig. 1). These cells extended from the fascia into the perifascicular perimysium in a centripetal manner. No significant changes were noted in the myofibers except for the presence of a few basophilic (regenerative) fibers in two cases (patients 1 and 2) and type 2-fiber atrophy in another case (patient 5). The macrophages were strongly PAS-positive and resistant to diastase digestion. They also stained strongly with the acid phosphatase reaction and immunohistochemically for

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hepatitis B (months)</th>
<th>Diphtheria–tetanus–pertussis–hemophilus influenza (months)</th>
<th>Polio (IPV) (months)</th>
<th>Measles–mumps–rubella (months)</th>
<th>Hepatitis A (months)</th>
<th>Time between biopsy and last vaccine (months)</th>
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<tr>
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<td>2, 4, 6, 12</td>
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<td>2</td>
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<td>4, 6, 16</td>
<td>13</td>
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<td>3</td>
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<tr>
<td>6</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Inactivated Polio vaccine.
CD68, but not for CD1A. The macrophages were not accompanied by other inflammatory cells except for rare T+ lymphocytes. Lymph follicles were present in one case (patient 4). No giant cells were seen in any of the specimens. Microorganisms could not be identified with stains for bacteria (Brown and Brenn), acid fast bacilli (Ziehl-Nilsen) or fungi (methenamine silver). No Birbeck granules or autophagic vacuoles were noted. Immunohistochemistry of dystrophin 1,2,3, laminin alpha 2 (merosin) and sarcoglycans alpha, beta, gamma and delta were normal in all biopsies. The infiltrate of macrophagic myofasciitis was impressive even though it was fairly localized. It was detected on paraffin section in all biopsies and on frozen sections in patients 1, 2, 5 and 6.

EM in case 1 demonstrated numerous irregular dense crystalline structures in the cytoplasm of macrophages (Fig. 2).

Energy-dispersive X-ray microanalysis demonstrated a specific aluminum peak in an area of macrophage cytoplasm inclusions (Fig. 3A, arrow) which was not present in a distant area (Fig. 3B).

4. Discussion

Even though most vaccinations are administered during infancy and early childhood, only a few children with macrophagic myofasciitis, ages of 1–14 years, have been previously described [5, 6, 11]. The present account of an additional six infants and young children may suggest that the prevalence of this entity in certain populations may be underestimated.

All six reported children presented at a very young age (2–18 months) and all were of Arab Moslem descent. While their clinical manifestations were variable and different from those of adult patients with this disorder, the pathological findings (including histopathology, histochemistry, immunohistochemistry and EM) were fairly standard and identical to those previously described in macrophagic myofasciitis [3]. Clinically, three of these children were evaluated to rule out a mitochondrial myopathy, and none had any pathological features that confirmed this disorder. In one child (case 3), decreased pyruvate oxidation was detected on polarography, which may suggest mitochondrial assembly or maintenance defect. Interestingly, this patient had myoclonic seizures and cognitive and speech delay but no clinical evidence of muscle disease such as motor delay, hypotonia or muscle weakness accompanying the pathological finding of macrophagic myofasciitis. The other three children underwent a muscle biopsy because of severe hypotonia and weakness. As a result of the ‘inflammatory’ nature of the muscle biopsy findings, two of them were treated with prednisone 2 mg/kg per day for 3 months with no improvement.

Four of our children exhibited central nervous system involvement: one 3.5-year-old with developmental delay and white matter abnormalities on magnetic resonance imaging (case 1), one 3-year-old with progressive myoclonic epilepsy and cognitive delay (case 3), an 11-month-old infant with global developmental delay in addition to severe hypotonia (case 5) and one 4-month-old with microcephaly, seizures, hypotonia and developmental delay (case 6). Developmental delay has been also previously described in children with macrophagic myofasciitis. Lacos et al. reported a 3-year-old with developmental delay and hypotonia [6], and Cabello et al. presented a 16-month-old...
boy with congenital hypotonia, delayed motor milestones and elevated serum creatine kinase [4].

Macrophagic myofasciitis has been recently associated with local reaction to aluminum compounds following vaccinations [5,6] and the evolution of this disorder as a new entity in France was related to the introduction of a vaccination program of hepatitis B in adults and to the fact that both the vaccinations and the muscle biopsies were performed in the deltoid muscles [6]. A similar situation occurs in children wherein muscle biopsies are obtained from the lateral thigh muscles where vaccinations are commonly administered. PCR to Tropheryma Whippelii was not performed due to absence of clinical findings suggestive of the diagnosis of Whipple disease.

Several lines of evidence have associated macrophagic myofasciitis with aluminum hydroxide-containing vaccines. Aluminum hydroxide has been previously linked to the formation of subcutaneous ‘granulomas’ [12]. Intracytoplasmic inclusions in the macrophages of macrophagic myofasciitis corresponded to aluminum hydroxide by microanalysis [5,6] and were shown to contain aluminum by atomic absorption spectrometry [5]. Finally, similar lesions were produced in rats following injection of aluminum hydroxide-containing vaccines [5]. Using energy-dispersive X-ray microanalysis, we confirmed the presence of aluminum compounds in macrophages (Fig. 3) in the one case in which this assessment was performed.

Aluminum hydroxide is found in various diphtheria–tetanus–pertussis, hepatitis B, hepatitis A, US military anthrax and most tetanus toxoid vaccines [13]. Aluminum is used as an adjuvant and serves as a potent stimulator of the immune system [13,14] and increases the duration of

Fig. 3. Energy-dispersive X-ray microanalysis demonstrating a specific aluminum peak in an area of macrophage cytoplasm inclusions (A, arrow) which is not present in a distant area (B).
the protective response [15]. Macrophage accumulations in injected sites decrease by 30 days and disappear from most sites within 3 months post-injection, although a residence time longer than 6 months has been observed in rats [9]. The low prevalence overall of this disorder and the probable inter-subject variability in the elimination of aluminum, led the WHO Vaccine Safety Advisory Committee to hypothesize that macrophagic myositis could occur in a predisposed subset of individuals with impaired ability to clear aluminum from the muscle [16].

Recently, macrophagic myositis was observed in identical twins [17] and was associated with HLA-DRB1*01 [18]. This, in addition to the relatively high incidence of this disorder detected in France and in consanguineous Moslem families in this report supports the assumption that it represents a genetic susceptibility to an inflammatory reaction triggered by aluminum.

While the association between aluminum and pathological findings in macrophagic myositis is well substantiated, its relation to the clinical manifestations in these patients is unclear. Several arguments support the notion that it is not necessarily the cause of the clinical manifestations. Aluminum intoxication has been mainly reported in patients with chronic renal failure undergoing hemodialysis [19]. Unlike macrophagic myositis, it is characterized by encephalopathy, osteomalacia and anemia. In vaccines, the quantity of adjuvant is limited to an amount that does not cause detectable changes in blood aluminum concentration [20]. It is also noteworthy that the presumptive diagnosis of adult patients with this disorder included myalgia, polymyositis and mitochondrial disorders which are, in any event, common indications for muscle biopsies [3]. The same applied to our children who were biopsied because of hypotonia or suspected mitochondrial disorders, which are very common indications for a muscle biopsy in infancy and early childhood. The clinical symptoms of children with macrophagic myositis are not necessarily acquired, and familial cases have been described [21]. Two of our patients were second cousins and 5 of our 6 patients had consanguineous parents. In case 1, 3 cousins from the father’s side died in early childhood and a sibling of patient 5 died from an apparently similar disease. Even more interesting is the fact that neuromuscular symptoms and signs were absent altogether in one of our patients (# 3). Thus, it seems that the clinical manifestations of children with this pathology do not comprise a unique clinical syndrome and may only reflect the different diseases that require a muscle biopsy.

We conclude that genetic predisposition probably accounts for the variability in the prevalence of macrophagic myositis in different populations. The clinical significance of this pathological syndrome is uncertain, and in children there seems to be no connection between macrophagic myositis as a pathological entity and the clinical symptoms and signs.

Acknowledgements

Mrs Esther Eshkol and Dr Malcolm Rabie are thanked for editorial assistance.

References