The Marden-Walker syndrome

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SUMMARY The characteristic facies, joint contractures, muscular hypotonia, and growth and developmental delay of the Marden-Walker syndrome were present in a 19-month-old boy. Extensive evaluation of the neuromuscular system failed to identify a specific abnormality. Electromyography was normal with low amplitude. Light and electron microscopy of a skeletal muscle biopsy was normal. Histochemical study of this biopsy material was also normal. The pathogenesis of the syndrome is discussed.

The Marden-Walker syndrome was first defined by Marden and Walker in 1966. In the past 10 years 5 additional patients have been identified (Fitch *et al.*, 1971; Temtamy *et al.*, 1975; Passarge, 1975; Simpson and Degnan, 1975). Retrospectively, the patients reported by Younessian and Ammann (1964) and Gellis (1963) have features of this syndrome. The infant described by Ealing (1944) may be the earliest description of the Marden-Walker syndrome. We report an additional patient with this syndrome.

Case report

The proband was born at 42 weeks' gestation after a pregnancy complicated only by a maternal weight gain of 21 kg. Birthweight was 2700 g with a length of 48.5 cm. Facial features were not specifically noted as dysmorphic at birth, but bilateral talipes equinovarus and camptodactyly of the fingers were noted. Delay of growth and development was apparent by 9 months of age. No unusual health problems were observed. The foot deformity was easily corrected with casting.

At present (19 months) the patient is below the third centile for all growth parameters: height, 76 cm; weight, 7.7 kg; and head circumference, 44.8 cm. Developmentally, the child rolls front to back and back to front. He sits unsupported for short periods of time. He rises on hands and knees. He does not crawl, but attempts to scoot. He does not stand alone or walk. He makes one or two distinct sounds, but not specific words.

The family history is negative for other individuals with a similar phenotype or partial manifestation of

the syndrome. The mother's age at delivery was 28 years, as was the father's. The mother has a normal daughter by a previous marriage. The first 2 pregnancies of the present marriage resulted in first trimester spontaneous abortions.

PHYSICAL EXAMINATION (FIG. 1 AND 2)

The mouth was small. Blepharophimosis with a depressed nasal bridge and a small nose were present. Intermittent exotropia was observed. The ears were marginally low set and the neck was short. The anterior fontanelle was 2 cm in diameter by palpation. Partly because of a decreased muscle mass, the trunk appeared large in relation to the small extremities. A grade 2/6 systolic ejection murmur was heard along the lower left sternal border. No organomegaly was present. The genitalia were normal, with descended testes. The neurological examination was grossly normal except for developmental delay, mild hypotonia, and mildly decreased reflexes. Camptodactyly of the left third and fourth digits and the right third digit at the proximal interphalangeal joints was observed. The fingers demonstrated arachnodactyly, and a unilateral transverse palmar crease was noted.

LABORATORY STUDIES

A complete blood count, urine analysis, and SMAC-20 were within the normal range. Metabolic screening of blood and urine was negative. Screening chromatography was normal. Creatinine clearance was 100 ml/min per m². A normal 46, XY karyotype was found with phytohaemagglutinin-stimulated peripheral lymphocytes and quinacrine banding.

RADIOLOGICAL STUDIES

The chest x-ray, IVP, barium enema, and skull films were normal. Bone age was 2 SD below the mean for

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Fig. 1 The proband at 19 months of age.

18 months of age. Bilateral radioulnar synostosis was noted.

NEUROMUSCULAR STUDIES

An electroencephalogram was abnormal, showing a repetitive spiking focus in the occipital area, most marked on the right side. Electromyography of the left gastrocnemius, tibialis anterior, and biceps, produced a wave form with low amplitude and brief action potentials. No fibrillations or fasciculations were noted. No myotonic discharges were found on electromyography. Muscle biopsy showed uniform diameter fibres with no necrosis, regeneration, or inflammation. Both histochemical type I and type II muscle fibres were present in a normal checkerboard pattern. No intracellular inclusions were seen with trichrome stain. Oxidative enzyme preparations were normal. Electron microscopy was normal.

Discussion

In 1966, Marden and Walker described a 2600 g girl with dysmorphic facies and severe blepharophimosis.

Fig. 2 Facial features of the patient.

The infant had joint contractures, arachnodactyly, growth and developmental delay. She died at 3 months of age from pneumonia. The necropsy identified microcystic kidneys and an anomalous connection of the inferior vena cava with the superior vena cava. This infant was considered to represent a new clinical entity, though some of the child's features were similar to those of the Schwartz-Jampel syndrome (Schwartz and Jampel, 1962; Aberfield *et al.*, 1970).

A second infant was reported by Fitch *et al.* (1971). This child had facies similar to the patient reported by Marden and Walker. Joint contractures, muscular hypotonia, and growth and developmental delay were also present. Pneumoencephalography showed reduced size of the brain stem and cerebellum, but not hypoplasia. Evaluation of the neuromuscular system with muscle biopsy and electromyography was performed. Again the syndrome was compared to the Schwartz-Jampel syndrome.

From Egypt, 2 first cousins with the same general phenotypic findings were identified (Temtamy *et al.*, 1975). This is the only familial occurrence of this syndrome reported so far. The family exhibited significant consanguinity. These findings suggest the possibility that this syndrome may be an autosomal recessive condition. Additional case reports in 1975 show similar phenotypic features (Passarge, 1975; Simpson and Degnan, 1975). The previously noted cases reported by Ealing (1944), Gellis (1963), and

Younessian and Ammann (1964), have some features of the Marden-Walker syndrome, but retrospectively the diagnosis is difficult to confirm.

The present case showed the typical features of this syndrome (Table). He had growth and developmental delay. The facies were similar with blepharophimosis, intermittent exotropia, a depressed nasal bridge, microstomia with pursed lips, micrognathia, and microcephaly. He did not have a cleft palate. Joint contractures were also a feature. Camptodactyly of the fingers, a finding not previously observed in this syndrome, was improving with regular extension exercises. Previously reported patients have also shown spontaneously improving or easily corrected joints contractures. Radioulnar synostosis, which has not previously been reported in this syndrome, limited pronation and supination of the forearm in this patient. Previous cases have had limitation of motion at the elbow joint, but no mention of the presence of radioulnar synostosis was made. Many infants have had arachnodactyly, as did the present patient. Muscular hypotonia and an apparent decrease in muscle mass have been found. Skeletal anomalies of the chest, such as kyphoscoliosis or pectus excavatum, have been previously observed, but were not present in this patient.

Major visceral anomalies have been identified in the kidney, heart, and brain in previously reported patients. Only the original patient reported by Marden and Walker (1966) showed renal anomalies. No other patients have had histological study of the kidneys. The present infant had a normal intravenous pyelogram, urine analysis, and creatinine clearance. He also had a cardiac murmur. The Marden-Walker patient had a cardiovascular anomaly of the inferior vena cava. One of the patients reported by Temtamy *et al.* (1975) had dextrocardia. All of the patients had

manifest developmental delay, but only the patient reported by Fitch *et al.* (1971) showed a structural abnormality of the central nervous system. The present child had an abnormal electroencephalogram.

Because of similarities to the Schwartz-Jampel syndrome, and because a previous patient (Fitch *et al.*, 1971) with the Marden-Walker syndrome had muscle abnormalities, the neuromuscular system was thoroughly evaluated in the present patient. Electromyography did not show significant abnormalities except for low amplitude. No evidence of myotonia was induced or identified. This is in contrast to the presence of myotonia in the Schwartz-Jampel syndrome (Schwartz and Jampel, 1962; Fowler *et al.*, 1974). Myotonia was also not present in the only other patient with Marden-Walker syndrome similarly studied (Fitch *et al.*, 1971). The histology of a skeletal muscle biopsy was normal in the present case. No disparity of muscle fibre size was identified, as had previously been reported by Fitch *et al.* (1971). Histochemical study of the biopsy was also normal, as was electron microscopy. The observed histochemical and ultrastructural changes of the Schwartz-Jampel syndrome were not present (Fowler *et al.*, 1974).

Both mothers reported by Temtamy *et al.* (1975) had had multiple spontaneous abortions. This suggests an increased fetal loss in families with the Marden-Walker syndrome. However, because of the consanguinity in this family other factors may have been important. The mother in the present case report had had 2 spontaneous abortions during her present marriage. None occurred during a previous marriage from which she had a normal daughter. This further suggests there may be an increased fetal loss with this syndrome.

Since only 1 instance of multiple family members with the Marden-Walker syndrome has been reported,

Table Phenotypic features of Marden-Walker syndrome

	Marden and Walker, 1966	Fitch <i>et al.</i> , 1971	Temtamy <i>et al.</i> , 1975	Temtamy <i>et al.</i> , 1975	Passarge 1975	Simpson and Degnan, 1975	Present case
Developmental delay	+	+	+	+	+	+	+
Growth failure	+	+	+	+	+	+	+
Facies	+	+	+	+	+	+	+
Microcephaly			+	+		+	+
Blepharophimosis	+	+	+	+	+	+	+
Strabismus	+	+					+
Micrognathia	+	+	+	+	+	+	+
Cleft palate	+					+	
Pectus and/or kyphoscoliosis	+		+	+	+		
Joint contractures	+	+	+	+		+	+
Talipes equinovarus	+	+					+
Arachnodactyly	+		+	+		+	+
Reduced muscle mass	+	+	+	+		+	+
Hypotonia		+	+	+		+	+
Survival	Died, 3 months	Alive, 9 months	Died, 2 years	Alive, 26 months	Alive, 9-5 years	Alive 3 years	Alive, 22 months

the genetic nature of the disease is far from clear. The Egyptian family reported by Temtamy *et al.* (1975) was consanguineous with 2 affected first cousins. This, of course, suggests autosomal recessive inheritance. The mean maternal age of 27 years, and the mean paternal age of 33 years in reported parents are above that of the general population. Advanced paternal age has been postulated as an important factor in new dominant mutations (Jones *et al.*, 1975). The mean paternal age in patients with this syndrome is similar to that observed in other known autosomal dominant conditions such as achondroplasia (Jones *et al.*, 1975). The present case is compatible with autosomal recessive inheritance, a new autosomal dominant mutation, or sporadic occurrence. Additional families must be studied to provide the necessary data for correct interpretation of the mode of inheritance.

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