

INTERMITTENT MUSCULAR WEAKNESS, EXTRASYSTOLES,
AND MULTIPLE DEVELOPMENTAL ANOMALIES

A New Syndrome?

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The co-existence of multiple anomalies in a patient has always attracted physicians' attention, particularly if the patient's appearance deviates grossly from normal. Usually in such a case an attempt is made to find a single pathogenic factor. In a few cases the diagnosis suggests itself to the physician already after his first glance at the patient. Examples of this kind include the syndromes of Marfan and Down. Most cases, however, are much more difficult to clear up and in a number of instances no definite diagnosis can be established.

In the following paragraphs the case history of an 8-year-old boy will be presented. He has several signs and symptoms suggesting a syndrome. However, on searching the literature, we have not been able to find a description which fits our case. It is hoped that this paper might prompt other physicians to report on similar patients.

CASE REPORT

The patient was born in June 1962. His mother had previously had four abortions, but has given birth to a normal girl in 1966. His father suffers from psoriasis. Otherwise, both parents are healthy. His mother's sister has primary amenorrhoea. Apart from that, the family history has revealed nothing of importance.

The pregnancy was complicated by a minor vaginal bleeding in the second month for which the mother was treated with hormone injections of unknown type. The boy was born at term and delivery was normal. His birthweight was 3 000 g. Several developmental anomalies were noticed soon after birth: a large, soft cranium with incomplete mineralisation of the frontal and parietal bones, a defect of both the soft and the osseous palate, a single transverse palmar crease of both hands, and cryptorchidism. Three months later, extrasystole was found at a local hospital, but no other cardiac signs or symptoms were present. Control at irregular intervals during the following years showed an unchanged frequency of extrasystoles. Physical development seemed to proceed normally; the boy was able to sit without support at the age of 7 months and he could walk 7 months later. Since an unsuccessful attempt at surgical repair of the palatal defect in 1964, the boy has been wearing a palatal plate.

In June 1969 the boy, now aged 7, was admitted to a local hospital after an episode of muscular weakness of 3 1/2 hours' duration during which he had been unable to raise his arms and legs. The most prominent finding was coupled ventricular extrasystoles, because of which he was digitalized. He was discharged on a regimen of digoxin 0.125 mg per day. This treatment did not seem to have any effect on the number of extrasystoles.

One month later he was readmitted after a short-lasting syncope and a dizzy spell followed by muscular weakness. No cyanosis, dyspnoea, convulsions, or nystagmus were noted. On June 15th, 1969, the patient was transferred to the Paediatric Department, Rigshospital, Copenhagen, for further investigation.

On admission he measured 110 cm, which is 18 cm below normal for his age. His bodyweight was 16.1 kg; this is 2 kg below normal for his height. His appearance was peculiar with scaphocephalic skull,



Fig. 1. Eight-year-old boy with low-set ears, hypertelorism, broad root of the nose, mandibular hypoplasia, and scaphocephalic cranium.

hypertelorism, low-set ears, broad nose, hypoplasia of the mandible, thin hair and slight bilateral ptosis (Fig. 1). Body proportions were normal. His fingers were short and pointed with an inward bending of the fifth fingers (Fig. 2) and his fifth toes were overlaid. His testicles could not be palpated. No cardiovascular abnormalities could be demonstrated apart from an irregular heart rate resulting from extrasystoles. There was no praecordial thrill and no significant murmurs. The second sound over the pulmonary area was normal. A phonocardiogram was also normal. An ordinary neurological examination disclosed weak patellar reflexes on both sides, but normal muscular strength and tone. There was no sign of dyscoordination and the cutaneous sensibility was normal.

An intraoral examination showed normal mucous membranes. In the central part of the palate a defect measuring $1 \times \frac{1}{2} \times 2$ cm was found, while the posterior part of the hard palate and the soft palate was characterized by cicatricial changes and by lack of uvula (Fig. 3).

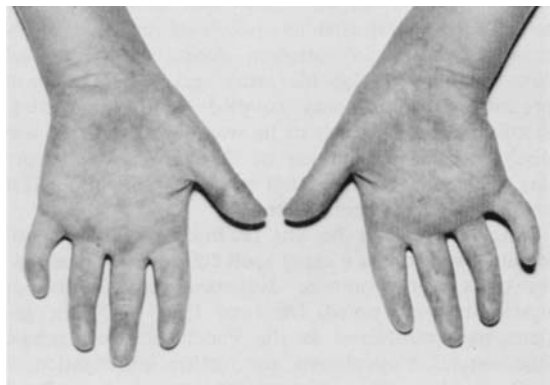


Fig. 2. Hands with short and pointed fingers, inward bending of the fifth fingers, and transverse furrow in the palms.

The following teeth were present (nomenclature according to Haderup (3)).¹

| | | | | | | | | | | | |
|----|----|----|----|----|----|----|----|----|----|----|----|
| 05 | 04 | 03 | 02 | 01 | + | 01 | 02 | 03 | 04 | 05 | |
| 6 | 05 | 04 | 03 | 02 | 01 | - | 01 | 02 | 03 | 04 | 05 |

All teeth were of normal shape and colour. There was a cross bite on +04, -04, +05, -05, 04+, 04-, 05+ and 05-, and 02+ was inverted lingually. There was an open bite in the front region measuring 4 mm. Radiological examination showed aplasia of 7-, 5-, 4-, -4, -5, -7, 1-, and -1. The stage of development of the tooth germs was late.

¹ According to the Haderup system of dental designation, + signifies the maxilla, - the mandible. If the symbol is placed to the right of the figure, the right side is indicated, and vice versa. 0 before the figure indicates a primary tooth.

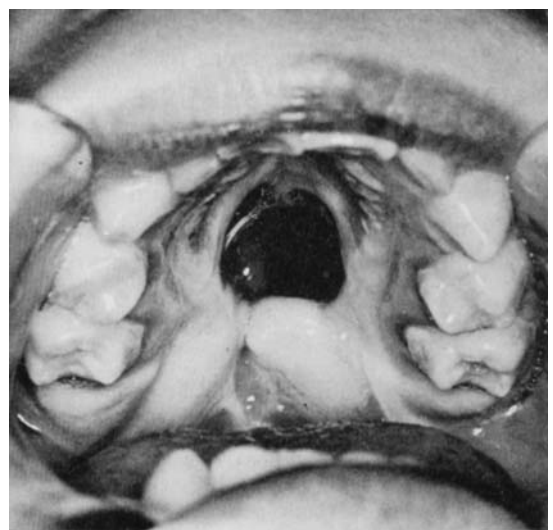


Fig. 3. Central defect of the hard palate surrounded by cicatricial changes after surgical intervention.

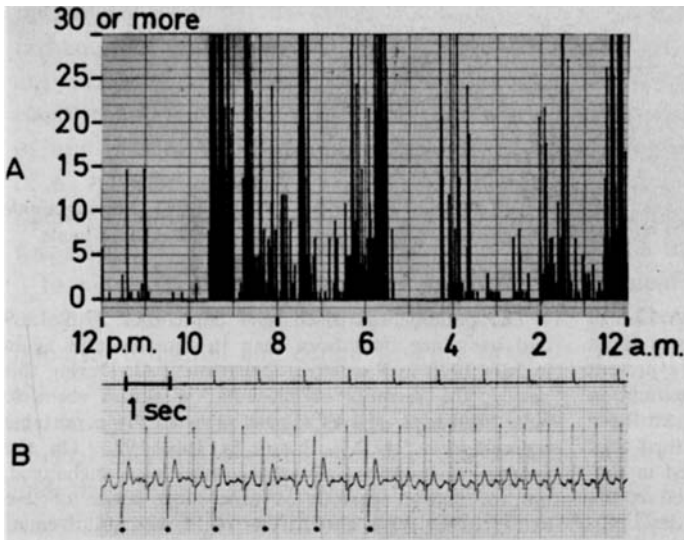


Fig. 4. (A) 12-hour histogram showing the number of ectopic beats per minute. Read from right to left. (B) Characteristic rhythm strip demonstrating a change from bigemini to normal sinus rhythm. Bipolar chest lead; ectopic beats indicated by dots.

The laboratory tests referred to below have been divided into different groups in order to evaluate the following diagnostic possibilities:

A. Chromosomal anomaly

cultures of both leucocytes from the blood and cells from a skin biopsy showed a chromosomal pattern as found in the normal male.

B. Neuromuscular disease

electromyography of the right biceps and left anterior tibial muscles and of the hypothenar muscles after repetitive stimulation of n. ulnaris disclosed no signs of neuromuscular disease. The blood concentrations of the following intracellular enzymes were all normal: glutamate pyruvate transaminase (0.5 units/liter), lactic acid dehydrogenase (LDH) (20 u/l), with a normal distribution of LDH-isoenzymes; aldolase (2.2 u/l), and alkaline phosphatase (78 u/l). The creatin phosphokinase was slightly, but not constantly elevated (141–45 u/l). The urinary excretion of creatin and creatinine was also within the normal range for his age: 50 mg and 390 mg, respectively. Serum potassium was 4.7 mEq/l. These investigations were carried out when the patient was free from symptoms.

C. Endocrine disease

the plasma level of protein bound iodine (5.1 $\mu\text{g}/100$ ml), the uptake of radioactive tri-iodothyronine by the patient's serum, and the urinary excretion of 17-keto-steroids (0.4 mg/day) and 17-ketogenic steroids (3.7 mg/day) were all normal. The administration of metyrapone resulted in an increased excretion of 17-ketogenic steroid in the urine (12.5 mg/day), and a significant fall of the plasma cortisol (1.5 $\mu\text{g}/100$ ml), while compound S increased (17.7 $\mu\text{g}/100$ ml). X-ray of the skull (including sella turcica) showed a relative underdevelopment of the facial bones and several ossa Wormiana, but was otherwise normal.

X-ray of the whole skeleton showed no abnormalities; the centres of ossification and the epiphyseal lines were normal.

D. Other investigations

Haemoglobin 14.2 g/100 ml. Leucocyte count: 4 300/mm³. Prothrombine time: 107%. Serum sodium: 146 mEq/l. Serum calcium: 10.4 mg/100 ml. Serum phosphorous: 5.4 mg/100 ml. Blood urea: 14 mg/100 ml. Serum creatinine: 0.6 mg/100 ml. Urine microscopy: normal. IgA: 0.93 g/l. IgG: 10.9 g/l. IgM: 0.41 g/l. Leucocytes for lysosomal enzymes: normal. Urinary excretion of amino acids and acid mucopolysaccharides: normal. An electroencephalogram was taken on three different occasions at approximately 6-month intervals, including tracings during photostimulation, hyperventilation, and slight dose. Real sleep was not achieved despite adequate sedation. All tracings were normal. Ophthalmological examination: normal. Audiometry: normal. The vestibular function was not investigated. Intelligence quotient: 96 (Binet).

E. Cardiac disease

because of multiple extrasystoles the patient was transferred to Medical Department B, Rigshospitalet, Copenhagen.

Cardiovascular findings were unchanged. Peripheral pulsation was normal. Arterial blood pressure was 110/70 mmHg. The chest roentgenogram showed a normal cardiac silhouette and pulmonary fields.

The ECG was monitored continuously by telemetry during the whole of his 7 weeks' stay in hospital. Multiple extrasystoles, probably of ventricular origin, were present most of the time. The percentage of extrasystoles varied from 0–84%, usually being in the range of 30–40%. A representative rhythm strip together with a 12-hour histogram is shown in Fig. 4. Occasionally series of 3–5 extrasystoles were noted (Fig. 5). Exercise was not consistently associated with

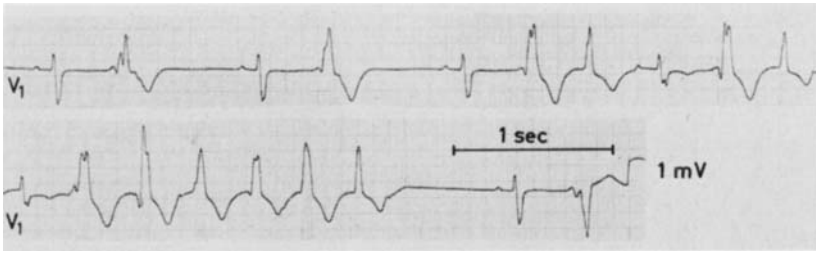


Fig. 5. ECG showing single and serial ectopic beats.

more extrasystoles than were present at rest. A 12-lead ECG was essentially normal, but sometimes a slight ST depression and inversion of T-waves were present in leads V₁ through V₃ (Fig. 6). On the assumption that his syncope and dizzy spell might have been caused by runs of extrasystoles, a therapeutical trial was undertaken. The following regimens, tried in succession over a period of 7 weeks, failed to reduce the number of extrasystoles: practolol 225 mg/day, propranolol 100 mg/day, and procainamide 1 g/day. *N*-propyl-ajmaliniumbitartrate (Giulini), a new drug which is not yet commercially available, in a dose of 20 mg/day did result in a reduction of the number of extrasystoles of about 75%. However, because of lack of experience with this drug, it was decided not to continue this therapy on a long-term basis.

He had no syncopes or dizzy spells during this admission. He experienced four episodes of muscular weakness, which were witnessed by the staff. On one occasion he was not able to raise his arms, on another, while walking around in the ward, he suddenly fell to the floor. He was not able to rise without help. He could walk, but limped. A considerable decrease of muscular strength in the right leg was clearly demonstrated when he tried to climb stairs. He was fully conscious during these episodes.

During such periods of muscular weakness, which were not related to any changes in the ECG, se-LDH (including iso-enzymes), se-aldolase, se-creatinin phosphokinase and se-potassium were normal. The attacks would last for a few hours. He had had these attacks since early childhood at intervals varying between 1–2 weeks to 1–2 months, each episode lasting 1/2 hour to 2 days. There was no constant relation to rest, physical activity, or meals. To investigate the latter possibility further, a glucose tolerance test including determinations of se-potassium was performed and was found to be normal.

The patient was discharged September 27th 1969 and has since then been seen in January and again in July 1970 in Paediatric Department G. During this period, the seizures of muscular weakness seem to have decreased. His ECG was recorded by a portable taperecorder for 2 1/2 hours in July 1970. On the average the number of extrasystoles was unchanged, but for shorter periods of time more series of 2–6 extrasystoles were noted. The child was still free of cardiac symptoms and had no syncopes. Physical findings were unchanged.

DISCUSSION

The most outstanding features of the present case are extrasystoles, seizures of muscular weakness, and multiple developmental anomalies in connection with a characteristic appearance. These findings naturally lead one to consider the presence of a syndrome, but we have not been able to find a similar combination of symptoms in the literature.

In a number of syndromes cardiac signs and symptoms are prominent (9). Holt-Oram's syndrome is characterized by a combination of disturbances of cardiac rhythm, atrial septal defect, and skeletal defects of the upper extremities (5). In our patient there was nothing to suggest the presence of a septal defect and the roentgenogram disclosed no malformations of the skeleton.

In Gorlin's "Leopard Syndrome" lentigo,

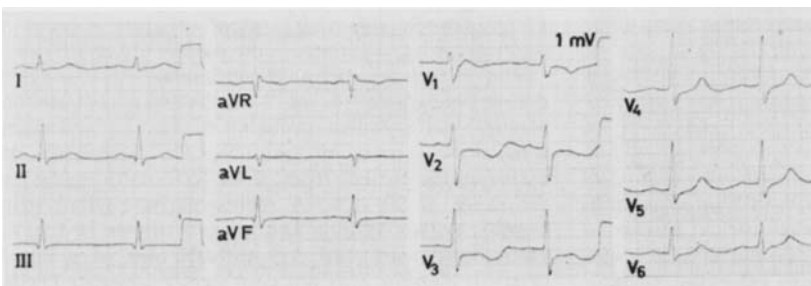


Fig. 6. 12-lead ECG at rest. Paper speed 50 mm/sec.

pulmonary stenosis, cardiac conduction disturbances of impulse formation and conduction are present (2). However, the physical findings, chest roentgenogram, and electrocardiogram in our patient did not support the diagnosis of a valvular anomaly. There were no lentigenes of the skin, and the patient's hearing was normal.

In neuromuscular diseases the myocardium is often affected, and often disturbances of impulse formation and conduction are present (5). The normal size and shape of the heart in this patient, together with an essentially normal ECG (in the absence of extrasystoles) and the absence of cardiac symptoms make the diagnosis of myocardiopathy unlikely.

In certain muscular diseases, as for instance the progressive muscular dystrophies, the blood concentration of intracellular enzymes such as creatine phosphokinase, aldolase, lactic acid dehydrogenase and glutamate pyruvate transaminase are markedly elevated (10). In our patient the elevation of the serum level of creatine phosphokinase was only slight and intermittent, and the levels of all the other enzymes mentioned were normal, also during periods of muscular weakness. The same apply to seropotassium, which together with the character of the episodes of muscular weakness speaks against a muscular disease associated with disturbances of potassium metabolism (adynamia episodica hereditaria, familial periodic paralysis (1, 2)). The urinary excretion of creatin and creatinine was normal. Furthermore, the electromyographic findings disclosed no abnormalities, which also speaks against the possibility of myasthenia gravis, which might have been suspected because of the intermittent character of the muscular weakness (6).

The possibility that the symptoms could be caused by an epileptic equivalent such as psychomotor epilepsy does not seem very likely. The EEGs were all normal, but unfortunately no curve was obtained during sleep. However, the symptoms were by no means characteristic of psychomotor seizures and the patient was fully conscious during the attacks.

Concerning the other characteristics of our patient, the reason for his dwarfism remains obscure. Plasma levels of protein-bound iodine and cortisol were normal, as was urinary excretion of 17-ketosteroids and 17-ketogenic steroids. Pituitary reserve of corticotropin was not decreased as judged by the metyraponetest. Sella turcica was of natural shape and size and skeletal development was not retarded.

The peculiar appearance of the patient's face has a certain resemblance to the syndrome of bird-headed dwarfism (8), but other essential features of this syndrome are missing (especially mental retardation). Further, this syndrome does not include any cardiac signs.

The palatal defect, the mandibular hypoplasia, and the aplasia of some of the teeth were of no further help in the classification of the patient.

In all the above-mentioned syndromes a hereditary factor seems to play an important role. The family history of our patient does not support this possibility. The pregnancy was complicated by vaginal haemorrhage in the second month and the mother was treated with hormones. This may, in an unknown way, have been of some importance for the pathogenesis of the developmental anomalies in our patient.

It is tempting to suggest that the presence in a child of symptoms and signs involving a number of organs and tissues be due to a chromosomal anomaly. Even if we have not been able to demonstrate one, this remains a possible explanation of the findings on our case as current techniques only allow visualization of very gross abnormalities of chromosomal structure involving several thousand genes.

SUMMARY

A description is given of an eight-year-old boy with extrasystoles, seizures of muscular weakness, and multiple developmental anomalies (dwarfism, scaphocephalic skull, hypertelorism, bilateral ptosis, low-set ears, broad nose, mandibular hypoplasia, aplasia of a number of teeth, defect of both the soft and os-

seous palate, inward bending of the fifth fingers, single transverse palmar crease of both hands, and cryptorchidism). These findings suggest a specific syndrome, but no similar description was found in the literature. The investigations disclosed no signs of either a chromosomal, a neuromuscular, or an endocrine disease.

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