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Pediatric Radiology

The Syndrome of Accelerated Bone Maturation in the Newborn Infant with Dysmorphism and Congenital Malformations

(The So-Called Marshall-Smith Syndrome)*

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Abstract. A new case of the syndrome of "accelerated skeletal maturation, facial dysmorphism, failure to thrive and psychomotor retardation" is presented. The syndrome was noted in the neonatal period. The diagnosis can be readily suggested by the radiologist because ossification centers show exceptionally early maturation. This case history increases to at least five the number of cases so far reported following the initial publication by Marshall and al. in 1971. If the two cases described in 1974 by Weaver and al. (as a distinct entity) are also included then the total of cases reported rises to seven.

Key words: Bones, dysplasias – Bones, primary disturbances of growth – Congenital malformations

In 1971, Marshall and col. [3] described two infants with a new syndrome characterised by the following triad of dysmorphism, extraordinary advance of bone age and failure to thrive. We wish to report the case of a patient who fits the description of the entity described by Marshall and col. with some minor differences. To the best of our knowledge it is the first case described in Europe.

Case Report

C. is the first child of non-consanguinous parents. The mother has been treated for the last two years with thyroxin (1 to 1.5 mg/24 h). This treatment was interrupted at the seventh month of pregnancy. On the mother's side four other women with a goitre have been found (the mother and three maternal aunts). The infant was mature and her birth weight was 3,800 Kg. Her height was not noted. On the second day of life, episodes of cyanosis during feeding led to the infant being hospitalized elsewhere. Due to the mother's history, congenital hyperthyroidism was considered even in the absence of goitre, cardiac signs, or hyperthermia. Radiographs of the hands, when 9 days old showed (Fig. 2) advanced skeletal maturation with ossification of 4 carpal centers.

Upon admission in our hospital the infant was 20 days old. She measured 53 cm (+ 1 DS) and weighed 3,700 Kg. The dysmorphic features were apparent with protrusion of the eyes, hypertelorism, antimongoloid slanting of the eyelids, cranio-facial disproportion with hypoplasia of the facial bones and micrognathia. There was frontal bossing with flattening of the base of the nose. The nostrils opened anteriorly; the philtrum was high; the hair was abundant. The ears were quite large, as were the hands and feet. The rest of the examination showed no evidence in favour of hyperthyroidism. A mass, found on the right flank, was related to hydronephrosis with a megaureter. Cyanosis during feeding was apparent. The different endocrine investigations performed, eventually contradicted the diagnosis of hyperthyroidism (T3, T4, total iodine, resine index, TRH test, I 131 fixation are normal). An elevated level of plasma testerone was found (133 mg/100 ml), the significance of which still remains uncertain. Serum Ca and P were normal. The mucopolysaccharides were normal. The caryotype was normal (46xx). The symptomatology was dominated by respiratory problems: the severity of the cyanosis at the time of feeding led to laryngoscopy which showed: "an abnormal configuration of the larynx with an increased length of the arytenoids". A Mayo canulla was introduced and this immediately improved the symptoms. On the 45th day a pleuro-pulmonary staphylococcal infection occurred which improved initially. At 75 days of age an attempt at fixation of the mandible to the hyoid bone was made so as to improve symptoms related to the mandibular malformation and glossolaryngeal malformation. However, the child died 48 hours after operation on 12. 8. 1974. At autopsy the pleuro-pulmonary staphylococcal infection was confirmed as was the hydronephrosis. Also an A.S.D. and hepatic venous congestive lesions were found. The tongue and the larynx appeared to have no morphologic abnormalities. The brain was not examined.

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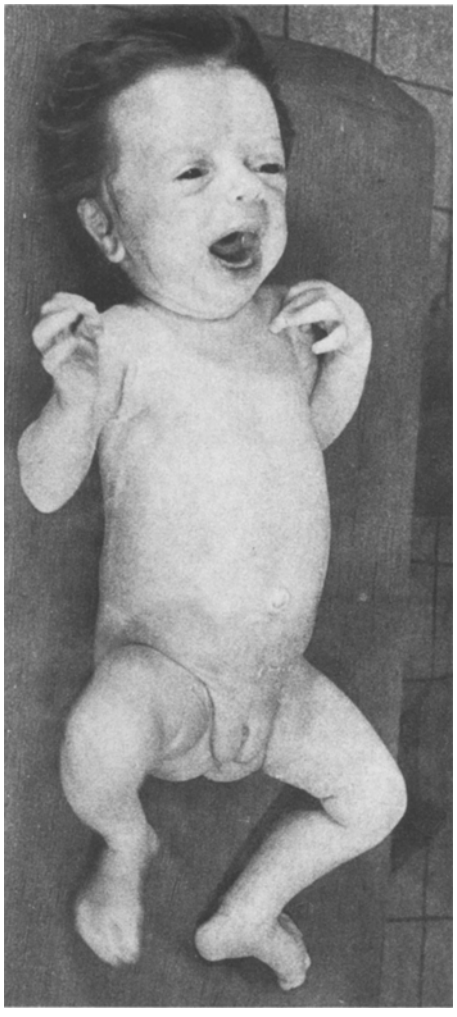


Fig. 1. The patient's photograph at age 20 days. The facial dysmorphism is obvious: ocular protrusion, hypertelorism, antimongoloid slanting of eyelids; micrognathia; frontal bossing; flattening of the base of the nose, with forward opening nostrils; high philtrum; hirsutism; large hands and feet; small umbilical hernia

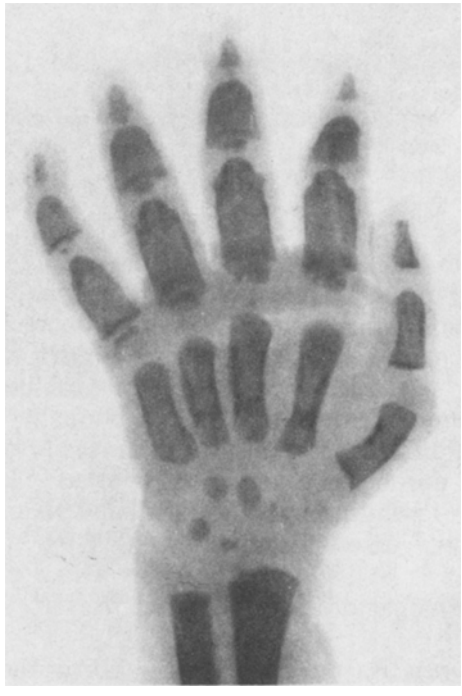


Fig. 2. Hand at 9 days: considerably advanced bony maturation. The morphologic abnormalities are already apparent: widening of the proximal and middle phalanges; the former have a rounded distal extremity. The first metacarpal is curved

Radiological Investigation

1. The Principal Finding is that of an Extraordinary Advance in Bony Maturation

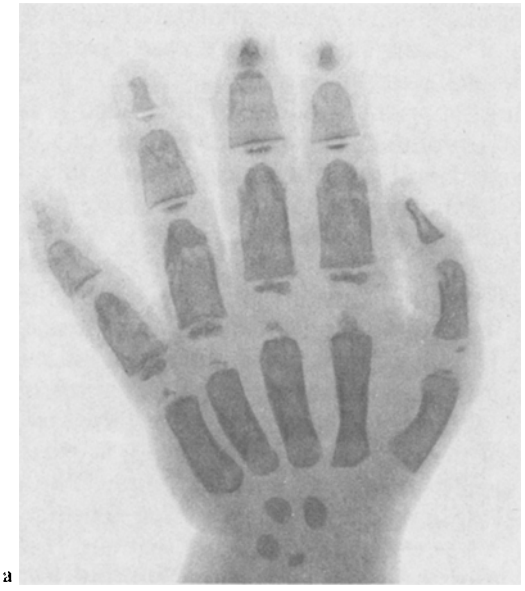
At 9 days of age, only radiographs of the hands and of both lower extremities had been taken (Fig. 2). In the hand, on each side, four carpal ossification centers, one metacarpal and eleven phalangeal centers can be noted. Bony maturation is that of a 18-24 month old child. The lower extremities show well-developed ossification centers in the knees and at the centers of the distal end of the tibia and fibula. Talus and calcaneus are well developed. Three centers are seen in the anterior tarsal bones: cuboid and cuneiforms. *At 3 weeks of age:* (Fig. 3a and b) a complete skeletal survey was performed. Eighty four ossification centers are present. At this age only 5 centers are usually found (variation between 4 and 8). Lefebvre's chart would indicate a bony age of over 6 years. In practice above 4 years of age the chart is no longer applicable. It therefore seems to us that trying to evaluate a bone age in the usual sense of the therm is not a valid exercise. However, one can extrapolate and postulate a bone age between 3 and 5 years by taking into account the nature of the ossification centers present.

It is quite remarkable to find that within 12 days 6 ossification centers appeared and that those centers present 12 days previously had matured further.

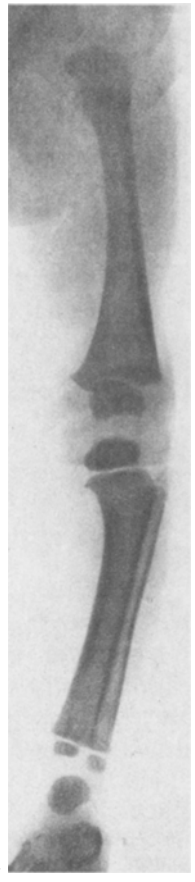
This rapid maturation is manifest by the ossification of the 5 sacral and 3 coccygeal vertebrae.

2. The Morphologic Abnormalities are also quite Unusual

The skull: (Fig. 4) shows an increased bitemporal diameter with thickening of the diploe particularly in the frontal area.



a



b

Fig. 3. a and **b** Radiographs of the extremities at 22 days of age: within 12 days, 6 new ossification centers appear in the hand. The morphologic abnormalities are again noted. The ossification centers of the long bones are spotty. The involvement is strictly symmetrical

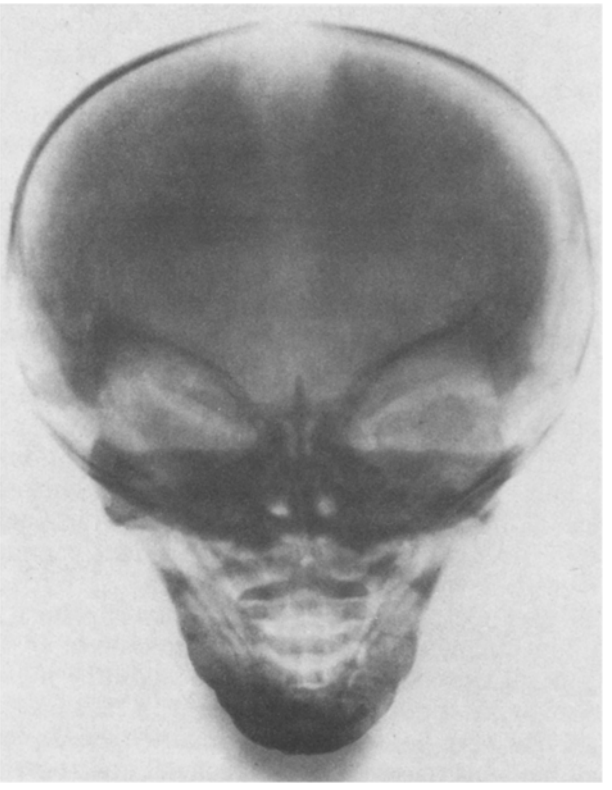


Fig. 4. Skull at 22 days. Widening of bitemporal diameter and thickening of the diplóe. The crista galli is completely ossified. Facial bones are small and micrognathia is obvious

The crista galli is completely ossified. The orbital cavities are shallow. The bones of the face are small and micrognathia is apparent. *The hands* are abnormal mainly through widening of the proximal and middle phalanges. At the level of the former, this abnormality is quite apparent with narrowing and rounding of the distal extremity (Fig. 2 and 3). On both examinations (day 9 and day 22) there seems to be a small change in the configuration of the 2nd and 3rd proximal phalanges for they appear on the last examination to be slightly less narrowed in their distal portion. Epiphyses are noted at the distal extremities of the first two metacarpals which are curved medially. *The bones of the feet* are of normal appearance apart from camptodactyly of the fourth left toe. *The epiphyses* are quite abnormal because of either a coarse irregularity [elbow, hip, knees (Fig. 3b)] or slight fragmentation (hands). In contrast, the carpal or tarsal bones show a normal configuration. The appearance of the ossification centers is symmetrical. A certain amount of diaphyseal narrowing is noted in the bones of the forearms and particularly of the radius but their metaphyses are normal.

The distal femoral metaphyses of both lower extremities are wide and there is a varus deformity of both proximal tibial metaphyses (Fig. 3b). The cortices are normal in appearance for the infant's age. The spine appears normal, aside from the advanced maturation. A slight scoliosis with right concavity is noted. The pelvis, ribs, clavicles, and scapula are all normal.

Discussion

The clinical and radiologic manifestations of this infant closely approximate to the cases published in 1971 by Marshall et al. [3], in 1973 by Tipton et al. [5], and in 1974 by Visveshwara et al. [6].

These patients, 3 boys and 1 girl all presented with a dysmorphic and radiologic syndrome identical to that observed in our patient.

Marshall et al. were the first to attract attention to this new syndrome: (i) peculiar facies, where ocular protrusion, shaggy eyebrows, hypoplasia of the nasal bones with nostrils orientated anteriorly, and hypoplasia of the face and mandible dominate; (ii) failure to thrive; and, (iii) extraordinary acceleration of bony maturation never previously observed in any other pathological state.

The next two publications confirmed the authenticity of this new syndrome by each contributing similar observations. A few additional clinical variants have been reported (choanal atresia uni- (5) or bilateral (6), hypertrichosis (6), rudimentary epiglottis (6)). These two patients died early from respiratory problems, one at 13 days (5), the other at 3 months (6). The last infant weighed only 3.150 gr at the time of death and measured 56 cm (the size at birth in the 4 patients reported was respectively 50, 63, 53 and 47 cm). The infant girl reported by Tipton and al. also had temporo-occipital macrogyria.

These 4 patients presented approximately the same *radiologic appearance.* Acceleration of bony maturation was apparent. We believe that acceleration of mineralisation of ossification centers is a more precise term. In every case mandibular hypoplasia was found as was widening of the middle phalanges or of the proximal and middle phalanges with distal thickening. Caryotypes were normal in every case. Neither biological nor particularly endocrine explanation could be found.

Recently Weaver [7] working with two of the co-authors of the initial publication (C. B. Graham and D. W. Smith) published two reports of patients also presenting with exaggerated growth, particular facies, camptodactyly and acceleration of bony maturation. The authors believed that they had presented another new syndrome. These patients had neither failure to thrive nor psychomotor retardation, nor widening of the middle phalanges. On the other hand excessive growth, hypertonia, widening of the bi-frontal diameter and widening of the femoral metaphyses were noted. These signs had not been previously described.

This distinction among the cases does not appear convincing to us. Facial dysmorphism is the same. The psychomotor development although estimated as normal appeared to be advanced in their first patient (at age 10 months, was appropriate to 18 months motor performance). On the other hand Visveshwara's case "seemed to have a satisfactory psychomotor development even though upright holding of the head was difficult at 4 months". Our patient had no neurological signs and psychological development appeared mediocre even though evaluation is quite difficult in this pathologic context. Weaver and al. [7] describe in both of their patients a muffled and raucous cry: this was also the finding in our patient and in Visveshwara's case. From the radiologic view point, our observations introduce certain features such as widening of the bi-frontal diameter, camptodactyly of the toes, widening of the femoral metaphyses, all of which were supposed to be characteristic of the "new syndrome" described by Weaver and al. Furthermore, if one compares, in our patient, the appearance of the phalanges at the 9th and 22st days, one can note the distal narrowing which appears to decrease between the two dates. One might expect that in some patients who have survived several months the abnormality of the phalanges could disappear. This abnormality is especially evident in all cases who are very young.

Our case has some distinctive features: there was extreme right hydronephrosis with megaureter. We would like to emphasize the maternal history: there was goiter in the direct antecedants of the mother. Also, the mother had been given some treatment with thyroxin during the first seven months of pregnancy. This background led to the suspicion of congenital hyperthyroidism: no clinical nor biological argument could confirm this suspicion. The infant's thyroid gland was normal at autopsy and histology. At the present time we are unable to say, if this is a coincidence or a predisposing factor. However, in none of the published cases was familial dysthyroidism described. Furthermore, cases of congenital [4] hyperthyroidism, if skeletal maturation is advanced, are not combined with this dysmorphic syndrome (other than the exophtalmos), nor with changes in the phalanges of the hand. Our case had a distinct elevation of plasma testosterone (133 mg/100 ml : N 30 mg/100 ml). The significance of this elevation remains to be elucidated.

Few conditions can be considered in the presence of such an advance in mineralisation of ossification centers associated with this dysmorphic syndrome. Apart from congenital hyperthyroidism there are peripheral dyostosis and facial dysmorphism of a pseudo-achondroplastic type with advance of bony maturation. These

children are small at birth with shortening of the extremities. The radiologic examination demonstrates cone shaped epiphyses in the phalanges of the hand and foot with shortening which affects mainly the metacarpals and metatarsals. Moreover, in the cases described, even if maturation is really advanced in the hand, it is never so in the whole of the skeleton. Any relationship between these distinct conditions remains to be established.

One of the fundamental questions raised by this new syndrome is to know (as emphasized by Marshall and others) if one is in presence of an authentic acceleration of bony maturation or, of an osteochondral dysplasia comprising rapid anarchic ossification of epiphyseal centers. Certain points are in favour of this second hypothesis such as the facial dysmorphism, indicating profound mesenchymal abnormalities, and, the absence of biochemical disturbances. We were impressed in our case by the extraordinary symmetry in morphology and localisation of the mineralised centers and by the irregularity of the epiphyseal centers. These findings favour a severe disturbance of mesenchymal origin producing for some unknown reason, rapid mineralisation of the epiphyses. Finally, it is surprising that this syndrome, which is so remarkable from a radiologic point of view, was not "discovered" until recently since the study of the skeleton is a routine procedure when there is neonatal distress or dysmorphism. Therefore, we suggest this condition is included in the Classification of the "Committee of Nomenclature of Intrinsic Diseases of Bone" [2] under the category number 9 in the group "disorganised development of cartilage and fibrous components of the skeleton".

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