Kenny-Caffey Syndrome

Case Report and Literature Review

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Kenny-Caffey Syndrome is a rare syndrome characterized by growth retardation, uniformly small slender long bones with medullary stenosis, thickened cortex of the long bones, hypocalcemia possibly with tetany at an early age, hyperphosphatemia, ocular abnormalities, and normal intelligence. We report a child with Kenny-Caffey Syndrome and idiopathic hypoparathyroidism and present a review of the literature summarizing the reported cases of this rare syndrome.

SINCE 1966, when the first two patients were described by Kenny and Linarelli,[1] only 21 cases of what has come to be known as Kenny-Caffey Syndrome have been reported.[1-10] Three of these have some features of Kenny-Caffey syndrome but lack medullary stenosis.[6]

Case Report

H.B., a 25-month-old Kuwaiti girl (Fig. 1), was referred at the age of 17 months for assessment of severe growth failure, persistent hypocalcemia, and recurrent tetanic convulsions.

She was born full term after an uneventful pregnancy with a birth weight of 2.7 kg. Her parents are first cousins and have four other normal children, but one boy died at birth and one girl died at the age of 3 months because of respiratory difficulties and hypocalcemia.

At the age of 13 days, H.B. presented to another hospital with tonic convulsions and was found to have a low serum calcium (1.5 mmol/L), a high phosphate (4.06 mmol/L), and a normal alkaline phosphatase (283 U/L). A normal RIA value for serum parathyroid hormone (PTH) (50 pmol/L) was obtained at the age of 45 days, and treatment was started with 1-α-cholecalciferol (0.5 ug twice daily) and calcium supplements (Sandoz, 1.7 g/kg/day). She continued to have persistent hypocalcemia, however, and was admitted several times with stridor, tetanic convulsions and hypocalcemia. Figure 2 shows the pattern of hypocalcemic convulsions since birth. At the age of 15 months, the parathyroid hormone RIA level (mid-molecule method),[11] was 84 pmol/L (nl 29–85) and 25-OH-Vitamin D level was 146 nmol/L (nl 15–100).[12] At 18 months, serum PTH was <100 ng/L (performed twice at the Hospital for Sick Children, London, U.K.) but 1-α-cholecalciferol had been temporarily stopped at that time.

On admission to our hospital at 17 months she was noted to be a very small girl weighing 3.8 kg, her length was 61 cm and fronto-occipital circumference (FOC) was 40.2 cm, all parameters below the 3rd percentile.

Physical examination revealed a rather triangular face, prominent forehead, open anterior fontanel (1.5 × 1.5 cm) and small deep set eyes. Fundoscopy was normal. She was edentulous. Examination of the chest, heart, abdomen, and genitalia was normal. The extremities were short relative to the trunk. Arm span was 54.5 cm; the upper segment was 40 cm and the lower segment 21.2 cm, consistent with micromelic dwarfism. The hands were small with short fingers, and the feet were short with prominent great toes. Developmentally, she was able to sit with support, stand when held, had a good pincer grasp, and could say three to four words with meaning, consistent with a mental age of 11–12 months.

The results of the laboratory investigations were as follows: Hemoglobin 115 gm/L, WBC 15.4 × 10^9/L (PMN 19%, L 71%). Serum calcium was 1.77 mmol/L, phosphate

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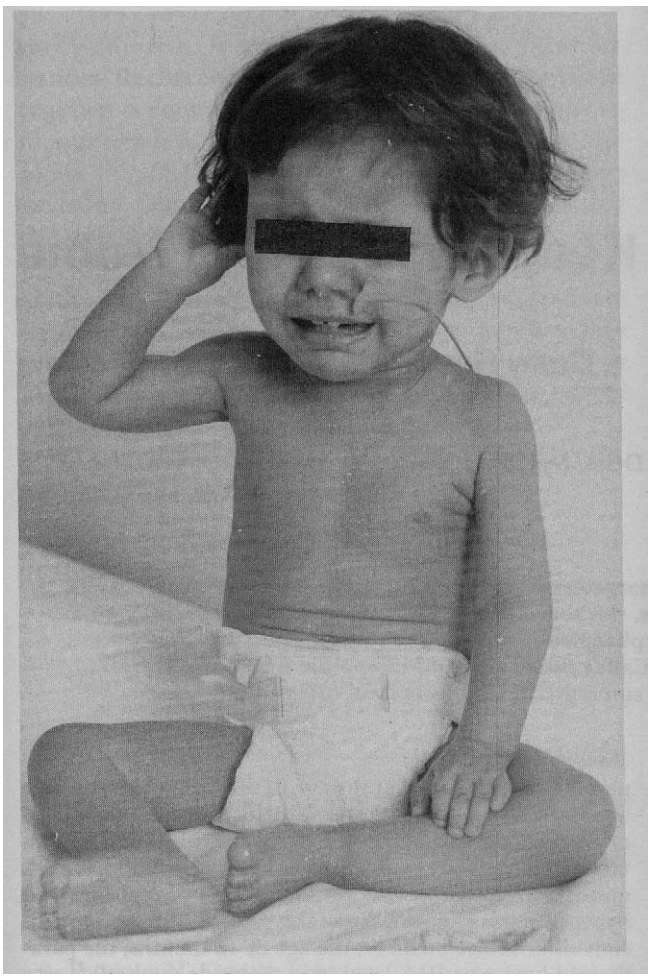

FIG. 1. Photograph of our patient with Kenny-Caffey Syndrome.

2.33 mmol/L, alkaline phosphatase 156 U/L. Serum magnesium was 0.74 mmol/L (0.74–0.99 mmol/L). Serum electrolytes were normal. Total proteins were 66 g/L, albumin 37 g/L, and the transaminases were elevated (ALT

FIG. 2. Serum calcium level at various ages. The arrows (↓) indicate periods of seizure activity. (Normal level = 2.2–2.6 mmol/L)

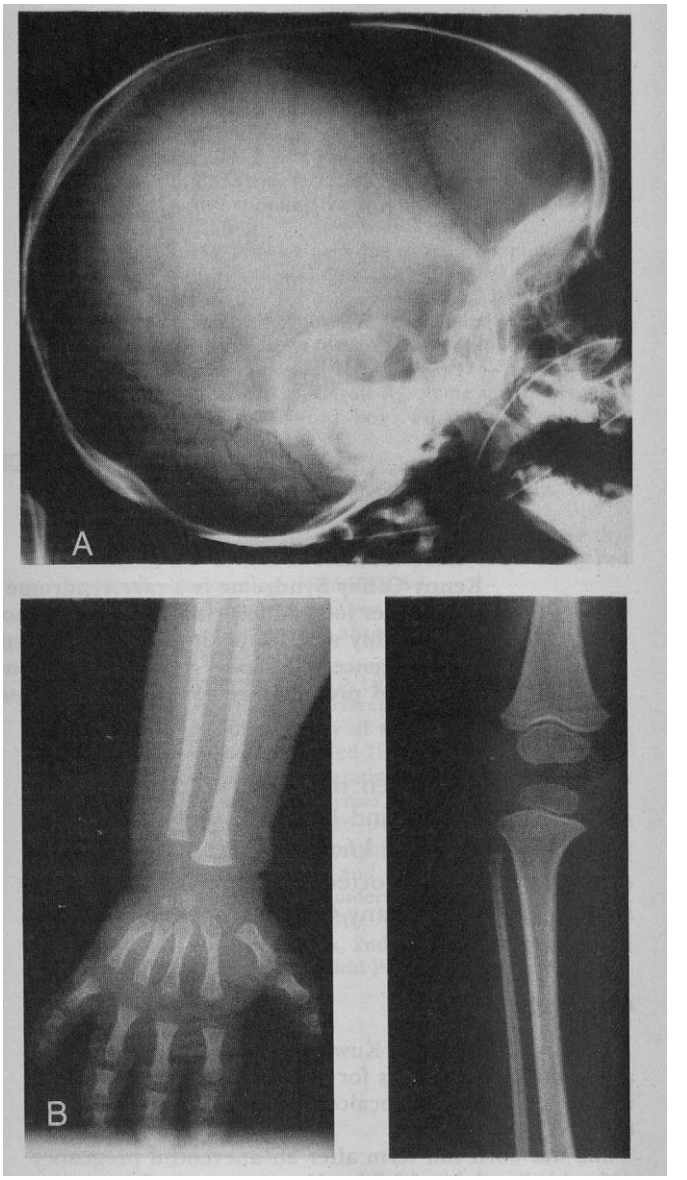

FIG. 3A and B. X-ray of skull and long bones showing: A. absent diploic space of calvaria; B. prominent tubulation of small bones of hands and medullary stenosis of radius, ulna, and long bones of the leg.

133 U/L, AST 283 U/L). Serum thyroxine was 91 nmol/L (91–103 nmol/L). Growth hormone assay was done by glucagon stimulation test[13] at another institution, and the results were: less than 0.5, 11, 13.1, 15.6, 6, and 3.8 ng/ml at times, 0, 60, 90, 120, 150, 180 minutes, respectively.

Radiologic studies showed the bone age to be consistent with that of early first year. The cranial bones revealed absent diploic space (Fig. 3A). The bones of the forearm and leg (Fig. 3B) showed considerable medullary stenosis. There was prominent tubulation of the long bones and of the small bones of the hands and feet. The distal phalanges were short and slender. There was no radiologic evidence

of pseudo-hypoparathyroidism or hypoparathyroidism. Radiologic studies for the rest of the family were normal.

Dr. John Caffey of Babies Hospital, New York City, was a pioneer in descriptive pediatric radiology. The Kenny-Caffey Syndrome described here differs clinically and radiographically from Caffey's Disease (infantile cortical hyperostosis), a previously more common entity, now only occasionally revisited (Clin Pediatr 26:177, 1987).

Her growth since birth is shown in Figure 4. Her growth continued very slowly despite adequate caloric intake by nasogastric feeds. Eruption of teeth (5 incisors, 4 premolars) began at 19 months, followed shortly by dental caries at 22 months. Her anterior fontanel is now closing at about 25 months. She has maintained normolcalcemia and has been seizure-free for the past 14 months.

Discussion and Review

Table 1 and 2 summarize the clinical, radiologic, and important laboratory findings in 22 patients with Kenny-Caffey Syndrome.[1-10] The most striking features (Table 1) include severe dwarfism, medullary stenosis, cortical thickening of the long bones, symptomatic hypocalcemia, ocular abnormalities, and normal intelligence. Our patient has most of the features described.

Proportionate growth retardation was the most commonly reported feature of the eight patients who were above 18 years of age; seven were below 3 standard deviations (SD) for adult height, and one within 2 SD.[1,3,5,6,9] Ten of the 12 patients with delayed bone age had proportionate dwarfism. Our patient had delayed bone age with micromelic dwarfism in contrast to the only other reported case of micromelic dwarfism[10] who had a normal bone age. Delayed closure of the anterior fontanel is also common, in some cases until the teenage years.[3,4]

The characteristic radiologic findings (Table 1) were first described by Caffey in 1967.[14] Majewski *et al.*[6] reported variability of expression in two different families; one family (3 cases) had features of Kenny-Caffey syndrome with medullary stenosis but none of that family had tetany. The second family had features of the syndrome with tetany but lacked medullary stenosis. This variability of phenotype is probably related to the degree of penetrance of the responsible genes.

Ocular anomalies were studied by Boynton *et al.*[4] A high degree of hyperopia and micro-ophthalmia were the most consistent ocular findings.[1,4,5,6,9,10]

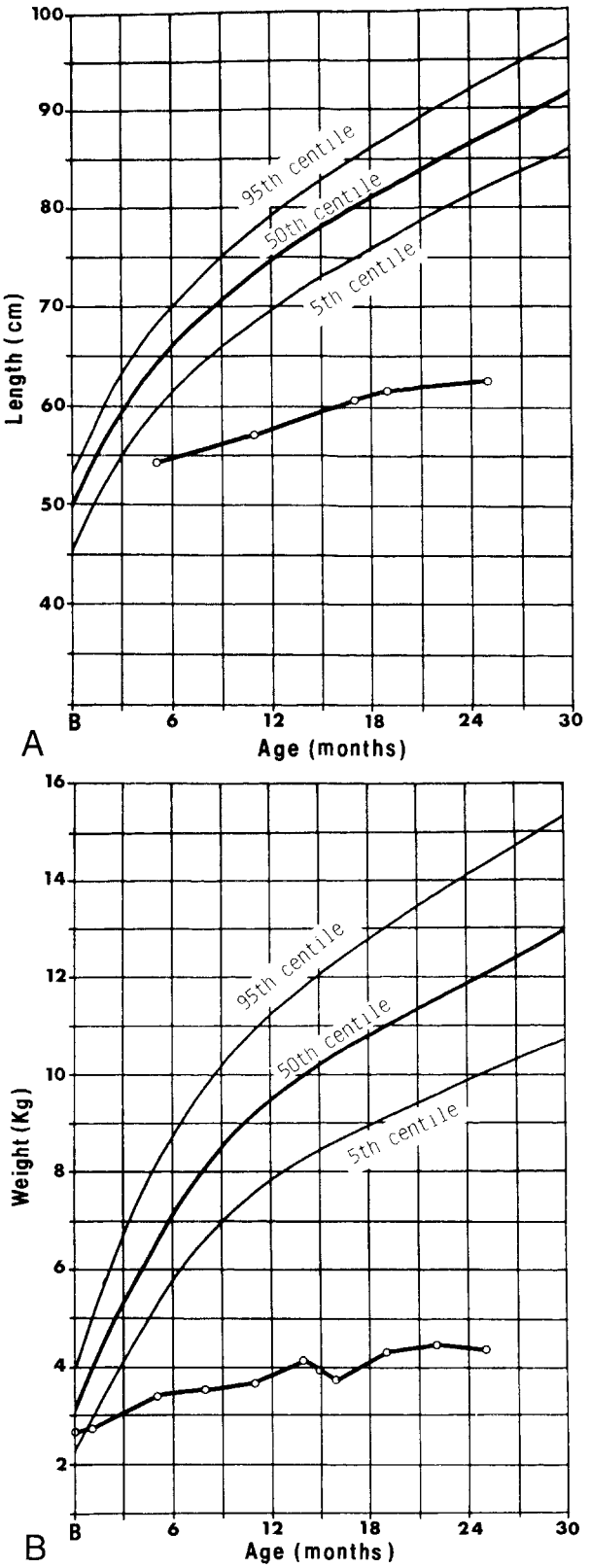

FIG. 4. Length, A; and weight, B, from birth to 25 months.

TABLE 1. *Summary of Clinical Features in 22 Patients with Kenny-Caffey Syndrome*

Feature[14]	Number of Affected Patients	Percentage	Our Patient
Age < 12 years (Mean age = 3.2 years)	12/22	55	2 years
> 12 years (Mean age = 28 years)	10/22		
Sex (male:female)	10/12		F
Birth weight (<2.5 Kg)	5/18	28	–
Short stature: Total	20/22	91	
Proportionate	18/20		
Micromelic	2/20		+
Delayed bone age[14]	12/20	60	+
Delayed closure of anterior fontanel[14]	16/18	89	+
Cortical thickening of long bones[14]	15/17	88	+
Medullary stenosis of long bones[14]	19/22	86	+
Absent diploic space in calvaria[14]	12/14	86	+
Dental caries	6/9	67	+
Ocular abnormalities Microophthalmia[1,3,4,5,6,9,10]	10/17	59	+
Refraction errors*	14/17	82	
Normal intelligence	15/17	88	±

* Hyperopia in 10/17; myopia in 4/17.

Other reported findings were strabismus,[3,5,6,9] pseudopapilledema,[1,4,5] congenital glaucoma,[5] the presence of myelinated nerve fibres in the fundi,[9] and band keratopathy.[4]

Hypocalcemia is a common finding in Kenny-Caffey syndrome (Table 2), with 59 percent having associated convulsions. The hypocalcemia was variable in expression, severity, duration, and age of onset ranging from a few days,[1,2,6,10] to several weeks, months,[4] even decades.[1] Fanconi *et al.*[10] reported a patient with abnormal PTH, who had surprisingly elevated PTH level in N-terminal radioimmunoassay (N-RIA) but undetectable PTH in carboxy terminal radioimmunoassay (C-RIA). Fanconi speculated that there are two major subgroups of Kenny-Caffey syndrome, one with hypoparathyroidism, the other without. Absence of features of pseudo-hypoparathyroidism in our patient with low PTH on two occasions are suggestive of idiopathic hypoparathyroidism associated with Kenny-Caffey syndrome.

Anemia was reported in only one-third of the patients and not felt to be related to medullary stenosis. Inconstant features were reported such as macrocephaly, prominent forehead, abnormal thickness of the skull, and dysmorphic features.

Out of 22 patients, nine cases were sporadic.[2–4,8–10] Six patients (5 boys, 1 girl) from five different mothers were described in four families.[1,5,6] Three

TABLE 2. *Summary of Laboratory Results in 22 Patients with Kenny-Caffey Syndrome*

Laboratory Test	Number of Affected Patients	Percentage	Our Patient
Hypocalcemia Total	16/22	73	
With tetany	13/22	59	+
Hyperphosphatemia	12/18	67	+
Normal alkaline phosphatase	11/11	100	+
Parathyroid hormone: Abnormally high[10]	1/13	8	
Normal[6]	6/13	46	
Low normal[9,10]	2/13	15	
Low[8,10]	4/13	31	+
High calcitonin[6,8,10]	2/10	20	
25 OH Vit D[8,9,10]: High	2/5	40	+
Normal	1/5	20	
Not detected	2/5	40	
1,25 di(OH) Vit D[8,9,10]: Normal	3/5	60	
Not detected	2/5	40	
Normal growth hormone[4,6,8,9]	6/7	86	+
Normal thyroid function[6,8,9]	9/9	100	+
Anemia	5/16	31	–

of these cases (1 boy, 2 girls) were born to mothers who have the disease.[6] These findings suggest autosomal dominant inheritance. Sarria *et al.*[5] reported two infants with a common father whose mothers were sisters without previous family history of Kenny-Caffey Syndrome. Similarly, our patient has a sister who died of hypocalcemia at 3 months and who probably had the syndrome, without a previous positive family history. This is suggestive of an autosomal recessive inheritance, but sporadic cases may be due to new mutations. This syndrome has been reported from different areas of the world and the familial cases are likely ubiquitously distributed and not restricted to one ethnic group.

Recommendations

The following recommendations are made regarding management of Kenny-Caffey Syndrome patients. They need regular careful follow-up, especially for calcium level monitoring, since the complications of hypocalcemia are potentially life-threatening. The patient may need supplementation, possibly throughout life. Regular visits to an ophthalmologist are important because of the high number of ocular anomalies found. Patients also should have regular dental check-ups as well as education regarding dental hygiene from the time of teeth eruption. Caloric requirements need to be evaluated periodically as well as regular assessment of growth. Force or tube feeding may be required to maintain good growth. Despite their short stature, these children may be of normal intelligence and therefore require proper evaluation for continued education and intellectual stimulation.

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