KENNY-CAFFEY SYNDROME TYPE 2: INSIGHT FROM TWO VIETNAMESE CASES

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We report two unrelated 8-year-old Vietnamese girls diagnosed with Kenny-Caffey Syndrome type 2 (KCS2), each harboring the same heterozygous pathogenic variant in the FAM111A gene (c.1706G>A, p.Arg569His). Case 1 presented initially at age 4 with poor growth and persistent anterior fontanelle. At age 8, she exhibited severe short stature (-4.5 SDS), macrocephaly, small hands, and craniofacial dysmorphisms. Additional findings included persistent fontanelle, hyperopia with amblyopia, cortical thickening of long bones, and asymptomatic hypocalcemia with normal parathyroid hormone (PTH) levels. Brain MRI showed a thin pituitary gland. Case 2 presented with short stature (-4.96 SDS), a history of hypocalcemic seizures, and congenital astigmatism. She had normal facial appearance but showed cortical bone thinning, absent pituitary lobes, and hypocalcemia with inappropriately low PTH levels. Despite calcium supplementation, normocalcemia was achieved only after calcitriol therapy. Growth hormone was later initiated with favorable growth response. Both cases underscore the variable expressivity of KCS2 and highlight the diagnostic value of genetic testing in children with unexplained short stature, skeletal anomalies, and calcium disturbances. The study contributed additional data on NKX6-2 variants in Vietnamese patients.

Keywords: Kenny-Caffey syndrome, severe short status.

I. INTRODUCTION

Kenny-Caffey syndrome (KCS) is a rare multisystemic disorder characterized by severe postnatal-onset proportionate short stature, cortical thickening of long bones, delayed anterior fontanelle closure, ocular and dental abnormalities, and variable hypocalcemia secondary to hypoparathyroidism.[1-4] First described in the 1960s, KCS is classified into two types based on genetic and clinical features. KCS type 2 (KCS2) results from heterozygous mutations in the *FAM111A* gene and follows an autosomal dominant inheritance pattern.[1,5] Fewer than 100 cases of KCS2 have been reported worldwide, with considerable variability in clinical expression.[2-4,6]

We report two unrelated Vietnamese girls diagnosed with KCS2, both carrying the same pathogenic variant c.1706G>A (p.Arg569His) in *FAM111A*. Both presented with severe short stature, hypocalcemia, and skeletal anomalies, though the extent of other features, such as ocular involvement and parathyroid dysfunction, varied. These cases underscore the importance of integrating clinical findings with genetic testing to ensure accurate diagnosis, especially in patients with atypical features and persistent unexplained hypocalcemia or growth failure.

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II. CASE REPORTS

1. Patient 1

An 8-year-old Vietnamese girl, first visited our pediatric endocrinology unit at the age of 4 due to concerns about poor growth and delayed

closure of her anterior fontanelle. At that time, no specific abnormality was identified except for calcifications found in both basal ganglia on a CTscan. No treatment was provided, and she did not return until her follow-up at 8 years old.

By her second visit at 8 years old, the patient presented with weight loss. She was noted to have severe short stature, with a height of 100.4cm (-4.5 SDS) while her mid-parental height was 160cm. She regularly followed up for transient hyperthyroidism management, which resolved after a few months of treatment without recurrence. Additionally, several abnormalities were observed, including distinct body features such as a relative large head circumference (50cm), a remaining anterior fontanelle of 4x4cm, small hands, high-grade hyperopia, amblyopia, and facial traits like deep-set eyes, a prominent forehead, and a pointed nose. Cognitive function was assessed as normal. Dental examination showed no hypo/oligodontia, enamel hypoplasia, or microdontia, but dental caries were noted.

Clinical laboratory tests were conducted to rule out conditions like Turner syndrome, assess thyroid function, and evaluate brain structure via MRI. Routine thyroid function assessments remained normal. Asymptomatic hypocalcemia was observed with calcium ion levels at 0.99 mmol/L; PTH was 22.5 pg/mL, suggesting intact parathyroid function. An MRI of the brain revealed a thin pituitary gland and a localized acute lesion in the corpus callosum. Karyotyping confirmed a normal 46,XX profile. Thyroid ultrasound and cardiac evaluations showed no abnormality. Bone age assessment indicated delayed skeletal maturation. Radiographs revealed cortical thickening and narrowed medullary canals in the long bones.

Given the patient's presentation of severe short stature, relative macrocephaly, delayed closure of the anterior fontanelle, severe myopia, and skeletal abnormalities, we strongly suspected Kenny-Caffey Syndrome and proceeded with genetic analysis.

Genetic testing confirmed the diagnosis of Kenny-Caffey Syndrome type 2, identifying a heterozygous pathogenic variant in the *FAM111A* gene (c.1706G>A, p.Arg569His).

2. Patient 2

An 8-year-old girl born in northern Vietnam was referred to our clinic in January 2023 for evaluation due to poor growth. At her initial examination, she was 102.2cm tall, which is 4.96 SDS below the mean. Her medical history included congenital astigmatism, episodes of seizures and hand cramps related to hypocalcemia.

Physical examination revealed no sign of dysmorphism or abnormal curvature of long bones. She was at Tanner stage 2 for breast development and stage 1 for pubic hair, with no vaginal discharge or menstruation. Her cognitive function was normal.

Laboratory tests showed low levels of ionized calcium (0.94 mmol/L) and total calcium (2.34 mmol/L), with slightly elevated serum phosphate (1.53 mmol/L) and normal magnesium (0.61 mmol/L). Karyotyping confirmed a normal 46,XX profile. Thyroid and adrenal functions were normal. A growth hormone (GH) stimulation test revealed a peak GH level of 2.33 ng/mL, and initial IGF-1 levels were normal at 101 ng/mL. Imaging studies showed a bone age matching her chronological age and absent pituitary lobes, suggestive of pituitary hypoplasia. X-rays revealed cortical bone thinning in the forearm and humerus.

Despite daily calcium supplementation at 100 mg/kg/day, her calcium levels remained low, with the lowest recorded level at 0.83 mmol/L. Hypoparathyroidism was not initially assessed,

but later tests indicated a low parathyroid hormone (PTH) level of 7.86 pg/mL. Calcitriol therapy was subsequently initiated to manage her hypoparathyroidism.

With her short stature, hypoparathyroidism, bone, and astigmatism issues, we suspected KCS and did genetic testing. Whole exome sequencing found a pathogenic variant c.1706G>A (p.Arg569His) in the *FAM111A* gene, confirming KCS. Growth hormone therapy at 25 mcg/kg daily was started along with calcitriol. She grew to 108cm (-4.1 SDS), gaining 5.8cm in five months. Hand cramps resolved with calcitriol, but reappeared immediately when the medication was inadvertently stopped.

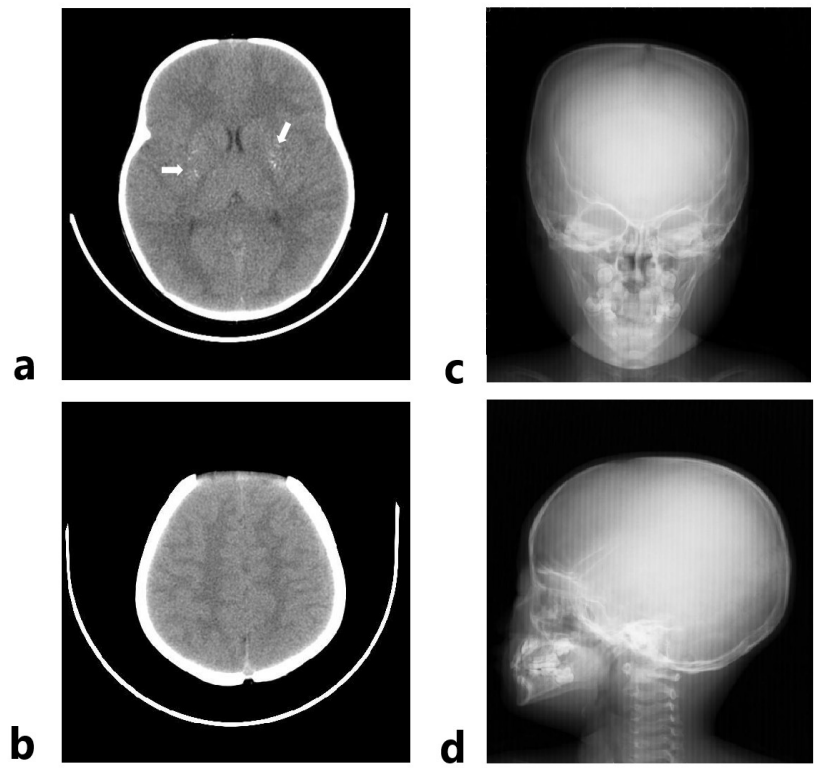

Figure 1. Imaging Abnormalities

(a) Basal ganglia calcifications indicated by white arrows (Patient 1, 2020); (b) Anterior fontanelle (width: 45 mm) at 4 years old (Patient 1, 2020); (c, d) V-shaped orbital roof visible on skull X-ray (Patient 2, 2019)

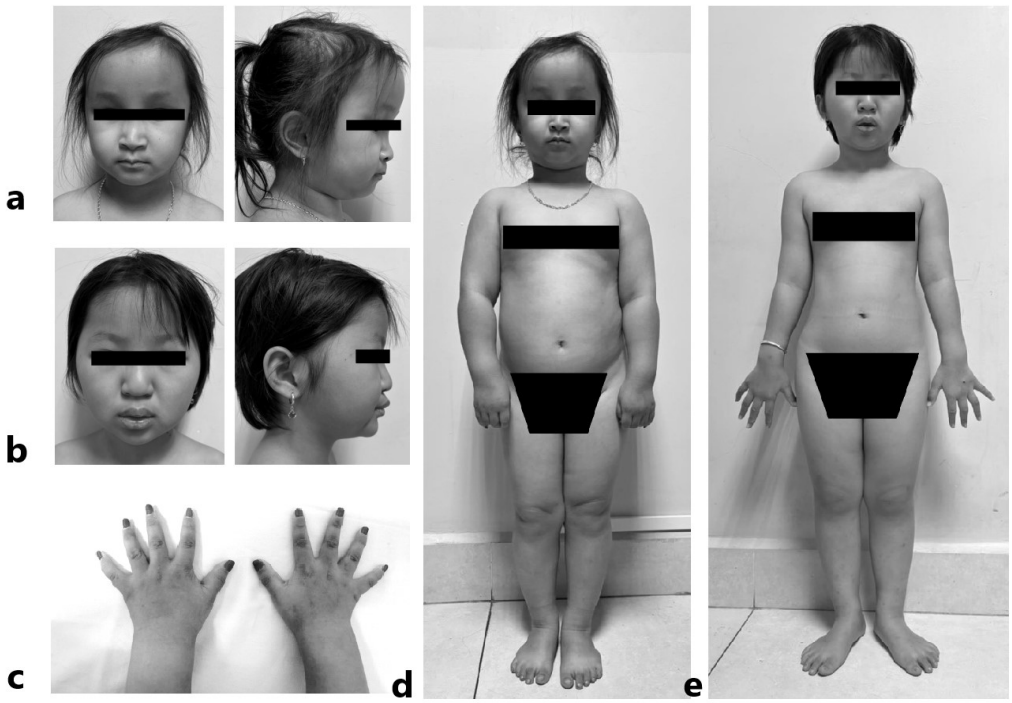

Figure 2. Phenotypic Findings

(a, b) Facial phenotype showing a large head, pointed nose, and deep-set eyes (Patient 1: a; Patient 2: b). (c) Relatively short fingers (Patient 1). (d, e) Images of Patient 1 and Patient 2 at ages 8 and 10 years, respectively, highlighting short stature and relatively small fingers

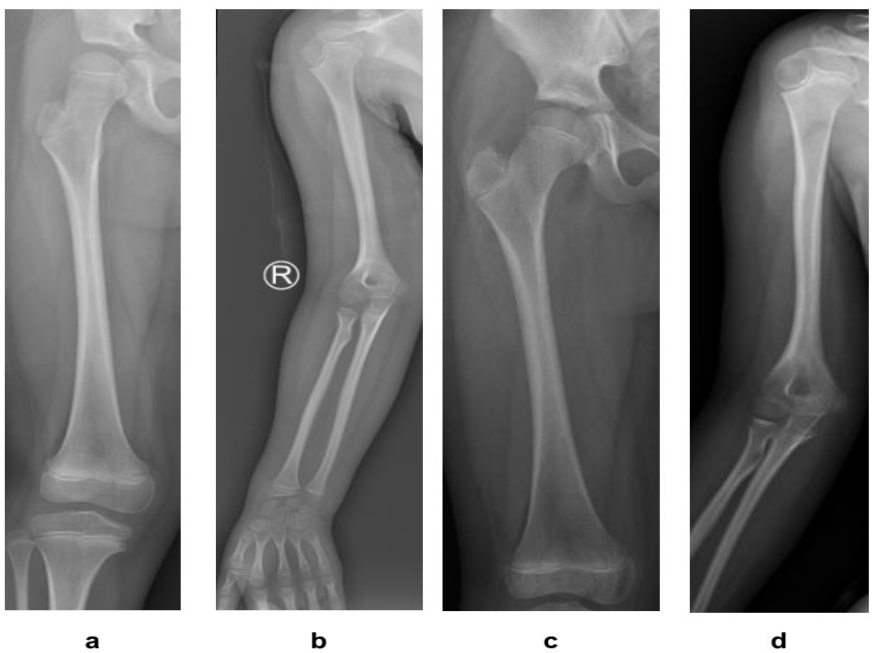

Figure 3. X-ray Images of Tubular Long Bones

Tubular long bones with reduced medullary space and cortical thickening (Patient 1: a, b; Patient 2: c,d)

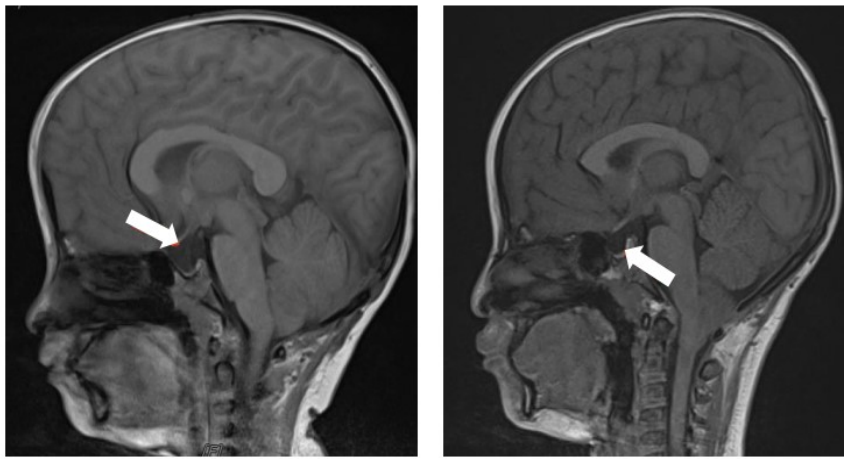

Figure 4. MRI Images of the Pituitary Gland

Abnormalities indicated by arrows (Patient 1: left, Patient 2: right)

III. DISCUSSION

Children with KCS2 are typically born at full term without intrauterine growth restriction, with postnatal growth failure emerging later on. Reported height deficits range from -2.6 SD to - 8.2 SD.[1] Our cases align with this pattern, as both children were born at term without intrauterine growth retardation and displayed significant short stature (-4.5 and -4.96 SDS, respectively). While GH deficiency was detected in our cases, not all previously reported KCS2 patients show this deficiency.[1] However, the exact mechanism remains unclear and is likely multifactorial, involving endocrine disruptions and skeletal development defects. For example, Patient 2, who began GH therapy at 8 years and 6 months, exhibited a growth response of 7 cm over 10 months, improving height SDS from -4.97 to -3.7 on a medium dose of 25 mcg/kg/day. Similarly, Abraham et al. reported a 6-year-old KCS2 patient with a c.1622C>A (p.Ser541Tyr) mutation in *FAM111A*, who responded to GH therapy with improved height velocity, albeit with normal baseline GH levels.[2]

Macrocephaly with relatively large head circumference compared to reduced height is a frequently noted feature in KCS2, often accompanied by frontal bossing and deep-set eyes.[3] Both of our cases exhibited these craniofacial traits, consistent with previous reports.[3,4] In contrast, microcephaly with intellectual disability is more commonly associated with KCS1 and can serve as a distinguishing factor. Cavole et al. documented a KCS2 case with microcephaly, suggesting phenotypic overlap with other syndromes like Sanjad-Sakati syndrome.[5]

A large anterior fontanelle with delayed closure is a recognized feature of KCS2, often due to impaired osteoblast function and defective bone matrix formation from *FAM111A* mutations, compounded by hypocalcemia affecting bone mineralization. Our Patient 1 first presented with an open anterior fontanelle at age 4, which remained at 4x4cm until age 8. For Patient 2, information on fontanelle closure is unavailable as the family did not recall this detail.

Craniosynostosis, often of the basal type resulting in a V-shaped orbital roof, has been noted in some cases, and was observed in both of our cases.[6] Additionally, cortical thickening

and stenosis of the medullary cavity in long bones are characteristic findings, with some individuals presenting with slender long bones.[4] These manifestations suggest that short stature in KCS2 is primarily linked to skeletal abnormalities rather than GH-IGF-1 axis dysfunction.[2]

Hypocalcemia is common in KCS2, often associated with hypoparathyroidism. In our cases, one patient presented with hypoparathyroidism. Chen and Zou reported hypoparathyroidism in 5 out of 8 KCS2 patients, while Schigt et al. found low PTH levels in 16 out of 20 genetically confirmed KCS2 cases.[1,4] Hypocalcemia in KCS2 can manifest early, frequently during the neonatal period, and often requires lifelong management with calcium and calcitriol supplementation.[6,7]

While basal ganglia calcification is not a defining feature of KCS2, it has been observed incidentally. Patient 1 exhibited basal ganglia calcifications on a CT scan of the anterior fontanelle, consistent with literature reports. However, this finding was not reassessed before publication, and Patient 2 has not undergone a CT scan for this evaluation. Primary hypoparathyroidism can result in hyperphosphatemia, which may lead to abnormal soft tissue calcification. Ning Yuan et al. also reported a case with multiple calcifications in the cerebral hemispheres and cerebellum linked to this variant.[8]

Ophthalmologic abnormalities, such as strabismus, nystagmus, myopia, hypermetropia, and astigmatism, have been reported in KCS2 patients, with visual impairment often progressing over time.[9] Both patients in our cases exhibited ophthalmologic symptoms, likely due to structural abnormalities associated with a V-shaped orbital roof.

Dental anomalies, including oligodontia, enamel hypoplasia, and delayed eruption, are also prevalent in KCS2, affecting over 60% of individuals.[3,5,6] However, our cases only presented with typical dental caries, with no further evaluation conducted.

Pituitary abnormalities have been less frequently documented in KCS2. Kyriaki et al. described a case with a small pituitary gland and empty sella, associated with a similar variant.[10] Both of our patients exhibited pituitary abnormalities on imaging. Additionally, our Patient 1 is the first reported case to present with transient hyperthyroidism instead of the commonly reported hypothyroidism in KCS2, potentially indicating an unrelated comorbidity. Both patients harbored missense mutations in the *FAM111A* gene, associated with autosomal dominant inheritance. Although no family history of abnormal stature or other symptoms was reported, Chen et al. identified nucleotide variant c.1706 as a mutational hotspot, predominantly associated with de novo mutations with similar clinical manifestations.[4]

IV. CONCLUSION

Our two cases of KCS2 demonstrate key features such as short stature, characteristic facial traits, cortical thickening of long bones, and hypoparathyroidism hypocalcemia. Both patients showed rare pituitary abnormalities, with one patient also exhibiting persistent anterior fontanelle enlargement. Genetic analysis confirmed *FAM111A* mutations, with the mutational hotspot c.1706.

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We declare that this research was conducted rigorously and independently without any conflicts of interest with any individuals or organizations

Image credits

The images were captured with the families' consent, and exclusively employed for scientific and educational purposes. Diagnostic images were conducted and archived by Department of Diagnostic Imaging, Vietnam National Children's Hospital.

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