RASopathies Are Associated With Delayed Puberty; Are They Associated With Precocious Puberty Too?

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RASopathies, such as Noonan, Costello, and cardio-facio-cutaneous syndromes, are developmental disorders caused by mutations in rat sarcoma–mitogen-activated protein kinase pathway genes. Mutations that cause Noonan syndrome have been associated with delayed puberty. Here we report 4 patients with either Costello or cardio-facio-cutaneous syndrome who developed precocious puberty, suggesting complex regulation of the hypothalamic–pituitary–gonadal axis and the timing of puberty by the rat sarcoma–mitogen-activated protein kinase pathway. Additional study of the timing of puberty among patients with RASopathies is warranted to ascertain the incidence of delayed and precocious puberty in these conditions and to examine genotype–phenotype correlations, which may provide insight into pathways that regulate the timing of puberty.

Despite recent advances,[1–3] many factors that regulate timing of puberty remain elusive. Rare syndromes associated with disorders in pubertal timing provide additional opportunities to identify genetic pathways that regulate the onset of puberty. RASopathies are developmental disorders caused by heterozygous activating germline mutations in rat sarcoma–mitogen-activated protein kinase (RAS-MAPK) pathway genes.[4,5] The RAS-MAPK pathway plays a central role in signal transduction from extracellular stimuli to the intracellular environment. The pathway is activated through hormones and growth factors that bind to tyrosine kinase, G-protein coupled, or extracellular matrix receptors. Binding results in phosphorylation and activation of proteins that control cell growth, differentiation, proliferation, and apoptosis, all critical aspects of normal development.[6,7]

RASopathies include Noonan syndrome (NS), Costello syndrome (CS), and cardio-facio-cutaneous syndrome (CFCS). These syndromes have overlapping features, such as craniofacial dysmorphisms; cardiac malformations; cutaneous, musculoskeletal, and ocular abnormalities; and developmental delay.[7] The overall incidence of RASopathies is 1 in 1000 to 2500 live births. NS is the most common condition. CS and CFCS are much rarer, with unknown exact prevalence.[8]

Although delayed puberty is described as a typical, although not universal, feature of NS,[9] little has been reported about pubertal timing in CS and CFCS. Delayed puberty has been described in CS,[10–13] and isolated cases of precocious puberty have been noted anecdotally in CS[14] and CFCS.[15–17] Unfortunately, only 1 of these articles describes clinical and biochemical data related to the

abstract

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DOI: 10.1542/peds.2016-0182

Accepted for publication Aug 9, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

To cite: van der Kaay DC, Levine B, Doyle D, et al. RASopathies Are Associated With Delayed Puberty; Are They Associated With Precocious Puberty Too?. *Pediatrics.* 2016;138(6):e20160182

TABLE 1 Clinical, Laboratory, and Imaging Characteristics of 4 Patients With Central Precocious Puberty

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Male	Female	Male	Male
Syndrome (gene mutation)	CFCS (*BRAF;* Asp638Glu)	CFCS (*KRAS;* Gln61Arg)[a]	CS (*HRAS;* Gly12Ser)	CS (*HRAS;* Gly12Ser)
Age at onset of puberty	4 y	3 y, 1 mo	7 y, 9 mo	8 y, 3 mo
Tanner staging at presentation	P2G3; TV 8–10 mL	P1B3	P1G2; TV 6 mL	P2G2; TV 5 mL
Height (SD score) at presentation	−1.9	−1.0	−2.4	−2.7
Basal,[b] poststimulation[c] LH level (IU/l)	NA; 38.6	NA; 38.8	1.3; NA	1.3; NA
Testosterone (nmol/l)[d] / Estradiol (pmol/l)[e]	T = 1.3	E = 226	T = 2.8	T = 1.9
Bone age at presentation	5.5 y	4.5 y	9 y, 9 mo	9.5 y
MRI	Mild asymmetry in ventricles, normal pituitary, nonspecific slight thinning of corpus callosum	No abnormalities	No abnormalities	No abnormalities, borderline Chiari I malformation
Additional and follow-up data				
Other endocrine diagnoses	None	GHD; primary amenorrhea	GHD	GHD
Age at last follow-up	10 y	18 y	16.5 y	13 y
Height (SD score) at last follow-up	−1.7	−3.6	−1.5	−2.7

NA, not available (not performed). Tanner staging: B, breast stage; G, genital stage; P, pubic hair; TV, testicular volume.

[a] The mutation found in this patient has not been reported previously as a germline mutation in a patient with RASopathy. The mutation was confirmed in DNA derived from blood and cultured fibroblasts from a skin biopsy. In these tissues there was no indication that the mutation was present in a mosaic fashion.

[b] Basal prepubertal LH level ≤0.2 IU/L.

[c] Poststimulation prepubertal LH level 3.3–5 IU/L.

[d] Prepubertal testosterone level <0.09–0.35 nmol/L (<2.5–10 ng/dL).

[e] Prepubertal estradiol level 18–74 pmol/L (5–20 pg/mL).

diagnosis of precocious puberty.[16] With research ethics board approval, we performed a retrospective chart review of 3 patients with CS or CFCS at the Hospital for Sick Children who presented with precocious puberty. After obtaining parental consent, specialists outside of the Hospital for Sick Children brought 1 other patient to our attention. The development of precocious puberty in these 4 patients provides new insight into the role of the RAS-MAPK pathway in regulation of puberty.

CASE PRESENTATION

Table 1 details characteristics of the patients. The elevated stimulated (patients 1 and 2) and basal luteinizing hormone (LH) levels (patients 3 and 4) indicate central activation of the hypothalamic–pituitary–gonadal axis, confirming the diagnoses of central precocious puberty (CPP).[18] Each patient displayed secondary sexual characteristics and bone age advancement. All patients received gonadotropin-releasing hormone (GnRH) analog treatment to suppress pubertal development.

DISCUSSION

We report a unique series of 4 patients with CS or CFCS and central precocious puberty based on clinical, laboratory, and radiologic investigations. Precocious puberty is traditionally defined as the onset of breast development at age <8 years in girls and testicular enlargement (≥4 mL) at age <9 years in boys.[19] Cases such as ours that are caused by central activation of the hypothalamic–pituitary–gonadal axis are referred to as CPP, the etiology of which can be idiopathic, familial, or secondary to structural brain anomalies such as hamartomas.[20,21] Within this scheme, our patients would be classified as having idiopathic CPP because slight thinning of the corpus callosum, seen in patient 1, is not regarded as a cause of CPP.[21,22] Furthermore, none of our patients manifested ventriculomegaly or hydrocephalus, structural anomalies that are known to be associated with CS or CFCS,[19,21] making it unlikely that elevated intracranial pressure played a role in the etiology of their CPP.

CS is caused by mutations in *HRAS,* and CFCS is caused by mutations in *BRAF, MEK1, MEK2,* and *KRAS.*[23,24] The RAS-MAPK pathway is 1 of the pathways involved in the regulation of the GnRH receptor signaling cascades.[25–27] GnRH receptor signaling results in secretion of LH and follicle-stimulating hormone from the pituitary gland and stimulation of sex steroid production by the gonads. Therefore, genetic abnormalities in this pathway could theoretically lead to either delayed or precocious pubertal development. However, it is important to note that the etiology of the precocious puberty in our cases is not fully defined. It remains possible that, in children with developmental delay, precocious puberty might occur as an indirect result of the gene mutation and derive from disease-associated hypothalamic dysfunction, which could occur even without causative structural brain abnormalities.[28]

Because the RAS-MAPK pathway is 1 of the intracellular signaling

pathways involved in growth hormone action,[29–31] it is perhaps not surprising that growth hormone deficiency (GHD) has been described in patients with RASopathies,[9,10,23] although as with precocious puberty the exact etiology of this association is not fully understood.

Reports of other cases of precocious puberty in patients with RASopathy indicate that our finding of CPP among patients with CS and CFCS is probably not a chance occurrence.[14–17] Together our data and these cases suggest that detailed investigation of the timing of puberty among patients with RASopathies is needed. Two cases of precocious puberty were noted among a cohort of 43 patients with CS[14] and 38 patients with CFCS[15]; however, the causes of precocious puberty could not be identified because of a lack of clinical and laboratory data, and it is not clear that pubertal timing was ascertained in all patients in these series. Çelik et al[16] recently documented CPP in association CFCS due to a *MEK1* mutation; this boy also demonstrated GHD without evidence of structural brain anomalies. An association between precocious puberty and the *BRAF* and *KRAS* mutation found in our patients with CFCS has not been described before.

Conversely, in a series of 17 patients with CS, White et al[10] reported a history of delayed puberty, absence of menarche, or normal age at start of puberty with primary amenorrhea in half of the patients, possibly because of central hypogonadism. Unfortunately, gene mutations were not documented, and comparison with our patients is not feasible. It is interesting in this regard that 1 of our patients developed primary amenorrhea of unclear etiology after cessation of her treatment of precocious puberty.

NS, typically associated with delayed puberty, is caused by mutations in *PTPN11, SOS1, RAF1,* and rarely with *KRAS, NRAS, SHOC2, CBL, RIT1, RRAS, RASA2, SOS2,* and *LZTR1*.[32,33] The gene mutations associated with NS seem to be distinct from the mutations linked to CS and CFCS. Therefore, we hypothesize that mutations in some genes of the RAS-MAPK pathway are more commonly associated with delayed puberty, whereas mutations in other genes may lead to CPP. The recent report of CPP in a boy with NS with multiple lentigines due to a novel mutation in *MEK1* (*MAP2K1*), a gene more commonly associated with CFCS, indicates that more work is needed to correlate specific gene mutations with aberrations in timing of puberty.[34] Although not the focus of our case series, another disorder that can be classified as a RASopathy, neurofibromatosis type 1, has been associated with CPP without structural abnormalities.[35]

Future comprehensive studies of pubertal development in patients with RASopathies are needed to investigate these important genotype–phenotype correlations. Such studies would provide insight into the pathways that regulate the timing of puberty and also ascertain the incidence of delayed and precocious puberty in these conditions. Because CPP may lead to adverse psychosocial functioning[29] and short adult stature, prospective monitoring and early recognition and treatment of CPP may improve long-term outcomes in patients with these disorders.

ABBREVIATIONS

CFCS: cardio-facio-cutaneous syndrome
CPP: central precocious puberty
CS: Costello syndrome
GHD: growth hormone deficiency
GnRH: gonadotropin-releasing hormone
LH: luteinizing hormone
NS: Noonan syndrome
RAS-MAPK: rat sarcoma–mitogen-activated protein kinase

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics 2016;138;
DOI: 10.1542/peds.2016-0182 originally published online November 23, 2016;

PEDIATRICS®
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