Kosaki overgrowth syndrome

Skeletal overgrowth accompanied by de novo heterozygous activating mutations in PDGFRB (platelet-derived growth factor receptor beta), that is, p.Pro584Arg and p.Trp566Arg, defines Kosaki overgrowth syndrome (OMIM #616592). Emerging evidence suggests a role of PDGFRB in the genesis of cerebral aneurysms. The delineation of the range and progression of the vascular phenotype of Kosaki overgrowth syndrome is urgently needed.

Takenouchi et al. conducted subsequent analyses of serial neurovascular imaging studies of two original patients with a de novo heterozygous mutation in PDGFRB, that is, p.Pro584Arg. The analysis showed the progressive dilation of basilar and vertebral arteries and coronary arteries commencing during the teenage years and early 20s. The radiographic appearance of the basilar vertebral aneurysms showed signs of arterial wall dilation, compatible with the known vascular pathology of vascular-type Ehlers-Danlos syndrome and Loeys-Dietz syndrome. The dolichoectasia in cerebrovascular arteries can lead to fatal complications, even with neurosurgical interventions. To prevent the progression of artery dilation, preventative and therapeutic medical measures using tyrosine kinase inhibitors may be necessary in addition to optimal control of the systemic blood pressure. Kosaki overgrowth syndrome is a clinically recognizable syndrome that can exhibit progressive dilatory and tortuous vascular changes in basilar/vertebral and coronary arteries as early as in the teenage years. They recommend careful counseling regarding the risk of future vascular complications, optimal blood pressure control, and regular systemic vascular screening during follow-up examinations [1)].

Three cases of KOGS, including a patient with a novel de novo variant c.1477A > T p.(Ser493Cys), and the oldest known individual age 53 years. The KOGS phenotype includes characteristic facial features, tall stature, scoliosis, hyperelastic thin skin, lipodystrophy, variable intellectual and neurological deterioration, and abnormalities on brain imaging. Long-term outcome is unknown. The cases confirm the phenotypic spectrum includes progressive flexion contractures, camptodactyly, widely spaced teeth, and constriction rings. We also propose novel occasional features including craniosynostosis, ocular pterygia, anterior chamber cleavage syndrome, early osteoporosis, increased pigmentation, recurrent haematomas, predisposition to cellulitis, nail dystrophy, carpal tunnel syndrome, recurrent hypoglycaemia in infancy, joint dislocation, and splenomegaly. Importantly, we report fusiform aneurysm of the basilar artery in two patients. Complications include thrombosis and stroke in the oldest reported patient and fatal rupture at the age of 21 in the patient with the novel variant. They conclude that cerebrovascular complications are part of the phenotypic spectrum of KOGS and KOGS-like disorders and suggest vascular imaging is indicated in these patients. [2)].

A 19-year-old Caucasian female with a history of hydrocephalus, Dandy-Walker malformation, cervical spine arachnoid cyst, progressive scoliosis, and overgrowth. Her physical exam included distinctive craniofacial dysmorphism, as well as soft and hyperextensible skin. Cardiovascular imaging during adolescence revealed saccular aneurysms in both coronary artery systems and subtle tortuosity of the cervical vertebral arteries. Exome sequencing trio analysis identified a de novo previously reported pathogenic variant in PDGFRB, c.1696T>C (p.[Trp566Arg]). Further functional studies included platelet-derived growth factor cellular metabolic pathway activity that confirmed the variant causes a constitutive activation of the PI3K-AKT pathway. This is the first report to characterize the

activating nature of this PDGFRB variant. They also highlight the connective tissue findings seen in Kosaki overgrowth syndrome and recommend baseline echocardiographic evaluation in all individuals with this condition with particular emphasis on coronary arteries [3].

References

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