

# New Ocular Associations in Sanjad-Sakati Syndrome

## Case report from Oman

Agha S. Haider,<sup>1</sup> Anuradha Ganesh,<sup>1</sup> Adila Al-Kindi,<sup>2</sup> Ahmad Al-Hinai,<sup>1</sup> Nadia Al-Kharousi,<sup>1</sup> Saif Al-Yaroubi,<sup>3</sup>  
<sup>\*</sup>Sana Al-Zuhabi<sup>1</sup>

## علامات جديدة بالعين ملتبزةة سنجاد سكاتي

تقرير حالة من سلطنة عمان

اغا شهاب حيدر، انورادا جانيش، عديلة الكندي، احمد الهنائي، نادية الخاروسي، سيف اليعربي، سنا الزهبي

**ABSTRACT:** Sanjad-Sakati syndrome (SSS; Online Mendelian Inheritance in Man [OMIM] #241410), also known as hypoparathyroidism-retardation-dysmorphism (HRD) syndrome, is an autosomal recessive disorder in which prenatal-onset extreme growth retardation, congenital hypoparathyroidism and craniofacial dysmorphism result from mutations in the *tubulin-specific chaperone E* (*TBCE*) gene on chromosome 1q42-43. We report unique ophthalmic findings in a two-year-old child with molecularly confirmed SSS, who was admitted to Sultan Qaboos University Hospital in Oman at 11 weeks old with bilateral congenital corneal clouding. The ophthalmic findings in this patient were linked to faulty microtubule assembly in the brain, abnormal intracellular membrane transport and the resulting metabolic derangement seen in patients with SSS.

**Keywords:** Sanjad-Sakati Syndrome; TBCE Protein, human; Corneal Opacity, congenital; Persistent Fetal Vasculature Syndrome; Nanophthalmos; Hypoparathyroidism; Case Report; Oman.

**الملخص:** تعد متلازمة سنجاد سكاتي (SSS; OMIM #241410) والمعروفة أيضاً بمتلازمة قصور الدريقيات-التخلف الذهني-العيوب الخلقية (HRD)، من الأمراض ذات الصفة المتنحية التي تظهر في فترة ما قبل الولادة في صورة تأخير شديد في النمو وقصور خلقي في وظائف الدريقيات وعيوب خلقية في منطقة الوجه والرأس والذي ينتج عن طفرة وراثية في الجين الخاص ببروتين الأنابيب المصاحب شيربون 1 (TBCE) على كromosome 1 الجزء 1q42-43. في هذا البحث تم توثيق علامات فريدة في عين طفلة في الثانية من العمر مصابة بمتلازمة سنجاد سكاتي المثبتة على المستوى الجزيئي الوراثي في مستشفى جامعة السلطان قابوس في عمان. تم ربط هذه العلامات بخلل في تجمع الأنابيب الدقيقة بالمخ مع وجود خلل في النقل عبر الأغشية داخل الخلية وما ينتجه من اختلال في عملية الأيض والذي يظهر في مرضي متلازمة سنجاد سكاتي.

**مفتاح الكلمات:** متلازمة سنجاد سكاتي؛ بروتين TBCE؛ عتمة القرنية؛ متلازمة استمرارية الأوعية الدموية الجينية؛ قزامة العين؛ قصور وظائف الدريقيات؛ تقرير حالة؛ عمان.

**S**ANJAD-SAKATI SYNDROME (SSS; ONLINE Mendelian Inheritance in Man [OMIM] #241410), also known as hypoparathyroidism-retardation-dysmorphism (HRD) syndrome, is an autosomal recessive chaperone disorder that is reported almost exclusively in patients of Arab ethnicity. First reported by Sanjad *et al.* in 1988,<sup>1</sup> SSS is caused by mutations in the gene-encoding *tubulin-specific chaperone E* (*TBCE*; RefSeq #NM\_003193), located on chromosome 1q42.3.<sup>2,3</sup> The disorder is characterised by congenital hypoparathyroidism leading to early onset hypocalcaemic seizures, prenatal onset of extreme growth retardation, mental retardation and craniofacial dysmorphism. Patients have a distinctive *facies* comprising of a narrow face, deep-set eyes, a beaked nose, large floppy ears, a thin upper lip and micrognathia.<sup>1,4</sup> Various ocular anomalies,

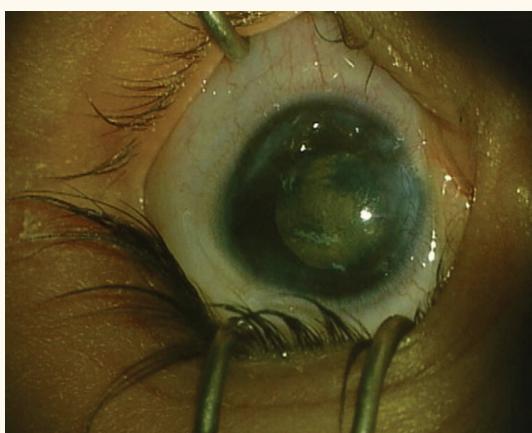
such as nanophthalmos, corneal opacification and retinal vascular tortuosity, have been reported in patients with SSS.<sup>5-7</sup> This case report highlights unique ophthalmic findings of spontaneously resolving corneal opacities and persistent fetal vasculature in a two-year-old child with molecularly-confirmed SSS. A hypothesis is proposed that links the ophthalmic findings in this patient to faulty microtubule assembly, abnormal intracellular membrane transport and the resulting metabolic derangement distinctive to SSS.

## Case Report

An 11-week-old infant girl presented to the Sultan Qaboos University Hospital, Muscat, Oman, with bilateral cloudy corneas which had been noted since birth. The infant's past medical history was significant

*Departments of*<sup>1</sup>*Ophthalmology,* <sup>2</sup>*Genetics and* <sup>3</sup>*Child Health, Sultan Qaboos University Hospital, Muscat, Oman*

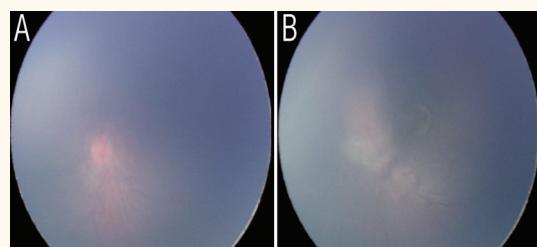
*\*Corresponding Author e-mail: zuhaibi@hotmail.com*



**Figure 1:** Image of the anterior segment of the patient's left eye showing patchy corneal opacification with peripheral scleralisation and 360 degree *pannus*. A yellowish reflex can be seen in the pupil, indicating the presence of posterior segment anomalies.

as she had severe growth retardation, with all growth parameters well below the third centile (weight: 4 kg; length: 48 cm; head circumference: 33 cm). The patient had recurrent episodes of hypocalcaemic seizures from the second week of life and recurrent hospital admissions for chest infections. She was the second child of consanguineous Omani parents and was born at 37 gestational weeks. She had a low birth weight of 1,500 g and was delivered by elective Caesarean section due to severe intrauterine growth retardation. A systemic review revealed a small-built infant with a beaked nose, long philtrum, thin upper lip, small pointed chin, large floppy ears and deep-set eyes. An ophthalmic examination of the patient showed normal vision at the light perception level, poor fixation and following in both eyes, with horizontal pendular sensory nystagmus. An examination of the anterior segment showed diffuse, dense corneal opacification; however, no further symptoms were visible.

On follow-up, the patient's corneal opacification was found to have partially resolved, with an improvement in corneal clarity. At the age of three months, the infant was examined under general anaesthesia. This assessment revealed that she had bilateral nanophthalmos (the axial length of her right eye was 14 mm, while her left eye was 12 mm) and central, patchy corneal opacification, with peripheral scleralisation and 360 degree *pannus* [Figure 1]. The anterior segments of the eyes were otherwise unremarkable. The pupillary reaction to light was difficult to determine due to her corneal opacity, but was believed to be sluggish in both eyes. An examination of the *fundus* revealed optic disc swelling and retinal vascular tortuosity in both eyes. The swelling was due to the presence of disc drusen



**Figure 2 A & B:** RetCam (Clarity Medical Systems, Pleasanton, California, USA) images\* of the (A) right and (B) left *fundus*. A: The right *fundus* shows a hyperemic elevated disc, tortuous retinal vessels and a tigroid appearance of the retina. B: The left *fundus* shows a large and dysplastic disc, peripapillary glial tissue extending temporally from the disc and a papillomacular fold.

\*Views are hazy due to residual corneal opacification.

in the right eye [Figure 2A]. In the left eye, the disc was dysplastic with extensive peripapillary gliosis. A papillomacular fold with shallow retinal detachment was seen in the posterior pole of the left eye [Figure 2B]. The intraocular pressure was 13 mmHg and 03 mmHg in the right and left eye, respectively. Features in the left eye were thought to be consistent with findings of persistent fetal vasculature (PFV) syndrome.

The child was later followed-up by clinical geneticists and paediatric endocrinologists. Biochemical investigations revealed low levels of parathyroid hormone (<0.1 pmol/L), with a low level of total calcium (1.97 mmol/L) and high levels of alkaline phosphatase (513 u/L) and phosphate (9.38 mmol/L). A skeletal survey showed that the child had severe osteopenia. Consequently, a supportive treatment plan, including vitamin D supplementation and growth hormones, was commenced.

This clinical and biochemical phenotype appearing in a consanguineous Omani family suggested the possibility of SSS. Thus, with the parents' informed consent, molecular genetic testing (real-time polymerase chain reaction using the melting curve method) was carried out, using primers specific for the c.155-166 12 base pair deletion in the *TBCE* gene on chromosome 1q42.3. The c.156-166 deletion in exon 3 was detected in both copies (homozygous) of the patient's *TBCE* gene. As yet, all cases of SSS reported in the Middle East have the same 12 base pair deletion, confirming its founder effect.<sup>2,4</sup>

## Discussion

The *TBCE* gene governs the synthesis of acytoskeleton-associated protein glycine-rich (CAP-Gly) domain at the N-terminus of the tubulin-folding cofactor E protein. This protein is required for microtubule assembly and stability and is ubiquitously

**Table 1:** A comparison of the characteristics of Sanjad-Sakati syndrome, Kenny-Caffey syndrome type 1 and the current case

Characteristic	Sanjad-Sakati syndrome	Kenny-Caffey syndrome type 1	Present case
Growth retardation	Intrauterine and postnatal growth retardation	Postnatal growth retardation only	Intrauterine and post-natal growth retardation
Mental characteristics	Mental retardation	Intellectually normal	Mental retardation
Head circumference	Microcephaly	Macrocephaly	Microcephaly
Hypoparathyroidism and hypocalcaemia	Hypoparathyroidism and hypocalcaemia	Hypoparathyroidism and hypocalcaemia	Hypoparathyroidism and hypocalcaemia
Infections/immunology	An increased susceptibility to infections in some patients due to hyposplenism and an impaired polymorphonuclear function <sup>b</sup>	Deranged cell-mediated immunity with recurrent bacterial infections	Recurrent infections; normal immune studies; but no detailed studies of polymorphonuclear or splenic function were reported
Bone characteristics	X-rays show demineralisation of bones; delayed bone age; there are reports of medullary stenosis and osteosclerosis in some patients	Osteosclerosis and thickening of long bones with medullary stenosis; absent diploic space in the skull bones	Demineralisation of bones; delayed bone age

expressed in all cells of the body. The c.155-166 deletion seen in this patient resulted in a deletion of four amino acids (p.Ser52-Glyc55del) in the CAP-Gly domain of the *TBCE* transcript. This eliminated the highly conserved glycine, which is adjacent to the essential residue for alpha-tubulin binding. This can result in a generalised aberration of microtubular polarity, intracellular transport signal transduction and cellular migration, which would explain the pleiotropic manifestations of SSS.<sup>2</sup> The homozygous deletions in the *TBCE* gene have also been reported in patients with Kenny-Caffey syndrome (KCS) type 1 (OMIM #244460).<sup>2,6</sup> This syndrome has a phenotype that resembles that of SSS but is characterised by slightly different clinical features, including normal intelligence, macrocephaly and deranged cell-mediated immunity [Table 1]. It is likely that KCS type 1 and SSS represent varying ends of the *TBCE* gene expression spectrum.<sup>3</sup>

Microphtalmia, nanophthalmos, hypermetropia, disk swelling and tortuous retinal vessels attributed to hypermetropia, pseudoduplication of the optic disc and *strabismus* have been reported in cases of SSS.<sup>5,7,9</sup> Corneal opacities have been noted in individuals with SSS.<sup>7</sup> However, their spontaneous resolution, as seen in the current patient, has not been reported. Other manifestations that have also not been previously described in SSS patients include posterior segment anomalies of PFV, such as disc dysplasia, peripapillary gliosis, papillomacular folds and shallow retinal detachment. In one study of eight patients with SSS, the predominant ocular finding was dense corneal opacities, abnormal retinal vessels and retinal vascular

tortuosity.<sup>7</sup> Papilloedema was reported in one patient, but no details were provided as to its cause.<sup>7</sup> Similarly, no supporting figures were provided. Previous studies have attributed the disc swelling, and other posterior segment abnormalities, to the nanophthalmos.<sup>5,6</sup> The authors of this case report believe that the disc swelling and vessel tortuosity, as well as the other retinal findings seen in this patient, are features of PFV. This condition can influence, either primarily or secondarily, the appearance of the optic nerve head and *macula*. Tractional deformation by the adherent fibroblastic or glial tissue can cause malformations of the optic nerve and macula,<sup>10</sup> as was also seen in the current patient.

The pleotrophic disease manifestations of SSS and KCS are related to deranged tubulin physiology, which affects tissues with abundant microtubules, such as the brain.<sup>3</sup> The ocular phenotype in SSS can also be explained in light of this knowledge. The authors of this case report postulate that mutations in the *TBCE* gene can cause a disturbance in microtubule function, which may explain the altered *apoptosis* and involution of the fetal vasculature. The tubulin microtubule system is known to play an important role in inducing the diverse signals responsible for the initiation of cell death.<sup>11</sup> Corneal opacities in patients with SSS may be caused by corneal calcium deposition as a consequence of the metabolic abnormalities that are a hallmark of this disease. The transient nature and spontaneous partial resolution of the corneal opacification in the current patient may be attributed to the prompt initiation of therapy and the improved serum calcium and phosphate levels.

## Conclusion

Unique ophthalmic findings of spontaneously resolving corneal opacities and PFV were observed in a two-year-old child with molecularly-confirmed SSS. A hypothesis is proposed to explain the pathogenesis of ocular anomalies seen in patients with SSS—the ophthalmic findings are thought to be caused by faulty microtubule assembly in the brain, abnormal intracellular membrane transport and the metabolic irregularities that are often seen in individuals with SSS. Reports of ocular findings in SSS patients are limited and the observations noted in this patient have not been previously reported.

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