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Ophthalmic manifestations and treatments of proteus syndrome: a case report and systematic review

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Abstract. – BACKGROUND: Proteus syndrome (PS) is an extremely rare disorder with ocular manifestations. In this study, we aimed to describe the ophthalmic characteristics and the clinical course of an unusual PS patient to acquire a comprehensive and intensive understanding of ocular PS and highlight the importance of collaborative treatment by ophthalmologists.

CASE PRESENTATION: A case of PS with atypical ocular features and syndromes was observed in a Chinese female. Her proptosis and vision impairment were relieved after Endoscope-Navigation system (ENS)-aided optic canal decompression. A 1.5-year follow-up showed that the treatment was temporarily effective, but the disease continued to develop. A review of the literature was conducted: forty-eight patients met the inclusion criteria. Although ocular manifestations play important roles in PS diagnosis, only a limited number of cases have been reported to have ocular abnormalities. And to date, almost none of these reports have described the treatment in detail. Therefore, PS patients with ocular manifestations were reviewed.

CONCLUSIONS: PS is a complex disorder with variable characteristics and progressive imbalances. In this paper, the clinical symptoms, molecular characteristics, and differential diagnosis of PS are introduced. More importantly, the ocular manifestations, treatment, and prognosis of PS cases to date are summarized and discussed. This study aimed to acquire a comprehensive and intensive understanding of ocular PS and to reveal the importance of collaborative treatment by ophthalmologists.

Key Words:
Proteus syndrome, Ocular, Ophthalmic manifestations, Ophthalmic treatments, Endoscope-navigation system (ENS).

Abbreviations

PS: Proteus syndrome; ENS: Endoscope-Navigation System; ICA: Internal Carotid Artery.

Introduction

Proteus syndrome (PS) was first described by Cohen and Hayden[1] in 1979. It is a very rare hamartomatous disease characterized by progressive segmental or patchy overgrowth in the skeleton, skin, and adipose tissue[1]. PS was first named by Wiedeman et al[2] in 1983 after the Greek sea god, who can transform himself into different shapes, representing the diverse clinical features of this disease.

PS is an extremely rare disease with a prevalence rate of approximately <1/1,000,000[3]. The characteristic of PS is the progressive mosaic or patchy overgrowth of several body regions, commonly affecting the skeleton, skin, adipose, and central nervous systems[4]. In most cases, manifestations develop rapidly from an early age[5]. A projected 25% mortality before 20 years of age was reported[6] by clinical research in a longitudinal natural history cohort. Regarding the histopathological features, the affected regions consist of normal tissue with an aberrant distribution and architecture. Researchers[7] have classified them into four types: lipomatous lesions, vascular anomalies, hamartomatous overgrowth, and sebaceous naevus.

However, the pathogenesis of PS is still unclear. A somatic mosaicism activating mutation of AKT1 (c.49G→A, p. Glu17Lys) was found[8] in most cases, indicating that abnormal activation of the PI3K-AKT pathway is the major cause.

Some cases[9-11] have reported ophthalmic complications related to PS, such as strabismus,

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nystagmus, high myopia, retinal pigmentary abnormalities, cataracts, rheogenic retinal detachment[12], glaucoma[13], and sector retinal dysfunction[14]. Ocular manifestations always show extensive ocular polymorphism[9]. As diagnostic criteria established by empiricism and published after many case reports appeared, Turner et al[15] reviewed and diagnosed 205 cases. In conclusion, although only 47.3% of cases in the predated literature met the latest PS criteria, PS cases had a higher incidence of ophthalmic complications than non-PS cases (42.3% *vs.* 13.8%), and ocular manifestations still showed large differences between patients.

Regrettably, few reports in literature have described ocular manifestations specifically, and no systematic review has concentrated on ocular features in the past 20 years. Moreover, many patients with ocular symptoms have received no specific ophthalmic examination or treatment[16]. Here, we describe a rare case of a 19-year-old female PS patient presenting vision impairment, proptosis, and strabismus. A PS case was reported in which the vision was preserved and restored, and the appearance improved after surgery for strabismus and optic nerve and orbital decompression under ENS. We are unaware of previous reports describing in detail ocular surgery performed on a PS patient and could find no reference to it in PubMed. Here, we summarize and discuss ocular features according to the currently available literature to provide ophthalmologists with a comprehensive understanding of PS.

Case Report

History

A 19-year-old female was referred to Ophthalmic Service because of the progression of blurry vision and exophthalmos. She was born to nonconsanguineous parents as a full-term neonate through vaginal delivery. She was already diagnosed with PS at 7 months of age by the pediatrician. Physical examination revealed a linear epidermal nevus and swellings and excrescences on her left face, including the frontal, orbital, zygomatic, and underjaw areas, accompanied by occlusal dysfunction and altered ocular motility (Figure 1). The progression of joint deformity, scoliosis, and asymmetric growth of her face and limbs caused her to undergo various surgeries, including epiphysiodesis twice, osteotomy of the right limb twice, meatoplasty of left aural atresia three times, resection of cerebriform plantar hyperplasia three times, and debulking surgery of extensive bony overgrowth of the frontal region twice. Continuous overgrowth in the skeleton was one of the most distinguishing characteristics of this PS patient. We found that several surgeries were performed a second or a third time because of relapse.

Ophthalmic Examinations

For almost a year, the patient observed a progression of exophthalmos and blurred vision of her left eye accompanied by lacrimation. Cycloplegic refraction showed visual acuity of 20/25 in the right eye (OD) and 20/100 in the left eye (OS), which improved to 20/20 (OD) and 20/50 (OS) after a refraction test was performed. The objective refraction was −1.24 dioptre cylinder (DC) × 165 (OD) and−0.50 DC/-2.00 DC × 165 (OS). The intraocular pressure was RT=20.3 mmHg and LT=19.3 mmHg. Fundus photography showed edema and congestion of the optic disc (OS). Proptosis was recorded to be 22 mm (OS) on Hertel's exophthalmometer (Figure 2A). The widths of the palpebral fissure are 28 mm (OD) and 32 mm (OS), and the heights of the palpebral fissure are 9 mm (OD) and 12 mm (OS). The anterior segment and fundus were normal except for macular edema of the left eye (Figure 2B), and a relative afferent pupillary defect was measured. Considering unilateral exophthalmos and a compressed optic nerve as cardinal signs of PS, we performed carotid artery CT angiography and enhanced MRI of the orbit. They showed abnormal lateral walls of the orbit, frontal sinus, ethmoidal sinus, sphenoidal sinus, and internal carotid arteries with abnormal routes in the intracranial sector and elongated optical canals. All these dysplastic structures led to compression of the optic nerves. Carotid artery CTA showed that the optic nerve was compressed by the internal carotid artery at the intracranial opening of the optic canal (Figure 2C).

Treatment

Orbital and optic nerve decompression was performed under general anesthesia by a transnasal endoscopic ethmoid sinus approach using an endoscope-navigation system. The wall of the optical canal was polished, and a thin, 2 cm-thick superior wall, medial wall, and floor of the orbit were resected. Adipose tissue under the periosteum and fascia was released. Next, a 2 mm-wide

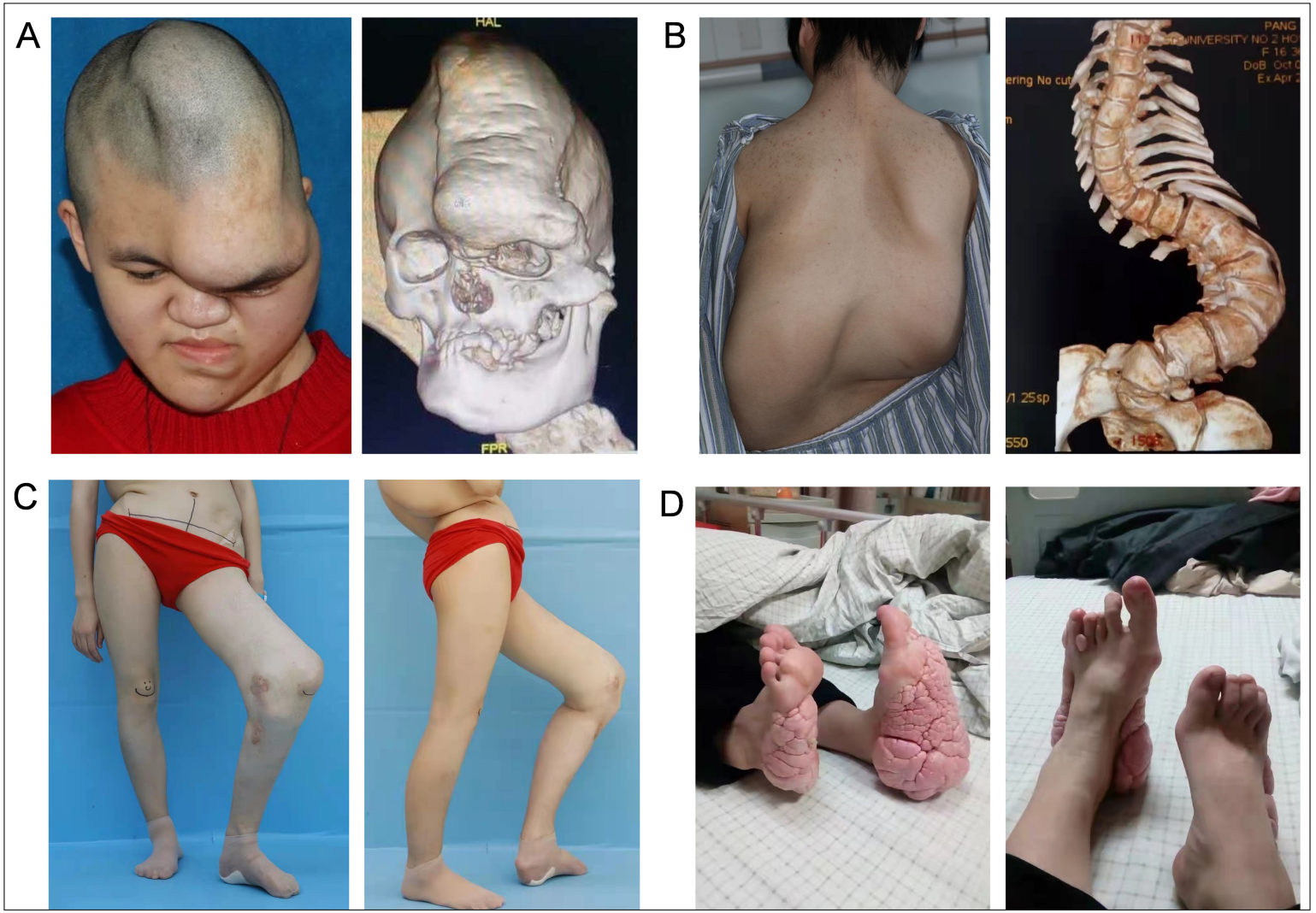

Figure 1. Clinical presentation of the current patient with Proteus syndrome before treatment. **A**, Facial photographs and three-dimensional model of the patient's skull before any cranial operations showed asymmetric and disproportionate hyperostosis of the skull and the external auditory canal. **B**, A back photograph and three-dimensional model of the patient's spine showed a linear epidermal nevus on the back and asymmetric and disproportionate overgrowth of vertebrae. **C**, Photographs and radiographs of the patient's lower limbs showed a linear epidermal nevus, and the right lower limb was longer than the left lower limb. **D**, Photographs of the patient's feet showed cerebriform plantar hyperplasia on both feet and enlarged toes with irregular bulges on the left foot.

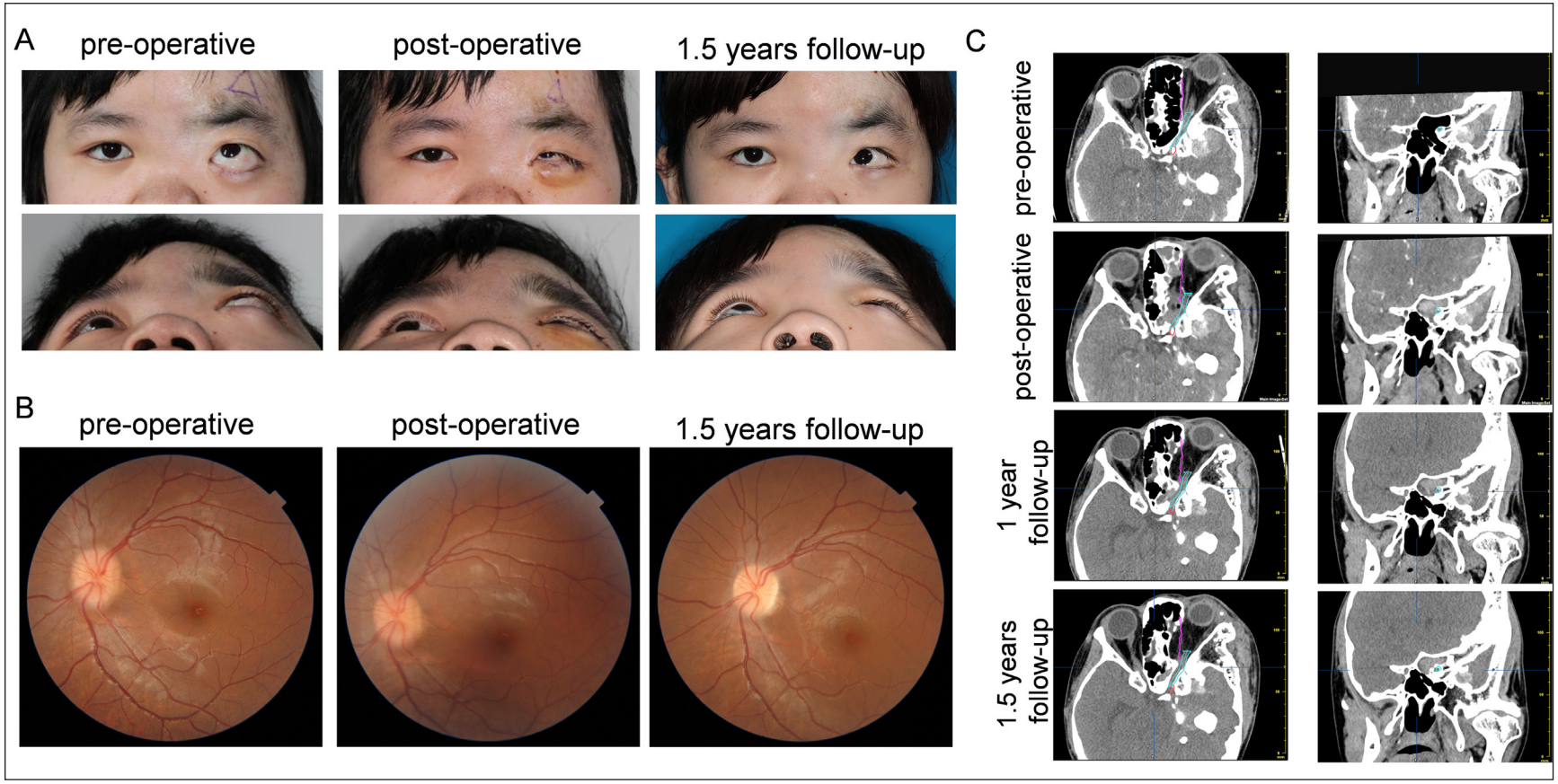

Figure 2. Ocular findings in the patient and outcome after ophthalmology surgery. **A**, Pre- and postoperative and follow-up facial photographs of the frontal view and from bottom to top showed that proptosis of the left eye was significantly improved after surgery. **B**, Pre- and postoperative and follow-up ocular fundus photographs showed changes in the fundus of the left eye. **C**, Pre- and postoperative and follow-up orbital CT scans showed the structures and morphology of the surgical site (red- internal carotid artery, blue- optic nerve, purple- medial orbital wall).

bitemporal floor of the orbit was resected through an infraorbital approach. One year later, the patient accepted strabismus diorthosis of the left eye under general anesthesia as a follow-up treatment, and the strabismus was remarkably relieved after the surgery.

Follow-Up

The surgery was fully successful. The proptosis of the left eye was significantly improved after surgery, but mild proptosis recurred after 1.5 years for the same reason (Figure 2A). The visual acuity increased to 20/50 (OS) 6 days after the operation and increased to 20/32 (OS) after 6 months, but it returned to 20/100 after 1.5 years because of the regrowth of the orbit. For macular edema and the relative afferent pupillary defect of the left eye, light relief occurred after the surgery and could not be measured in the follow-up period (Figure 2B). We observed complete decompression of the internal carotid artery and optic canal bone as designed (Figure 2C). It was effective throughout a one-year follow-up, while the medial orbital wall began to regrow, and the optic nerve and Internal Carotid Artery (ICA) became recompressed in the latest follow-up because of the continuous overgrowth of the skeleton (Figure 2C).

Discussion

Here, we report a PS case with optic nerve compression caused by progressive optic canal dysplasia and an extended internal carotid artery. Moreover, vision impairment by dysplastic optical canals and possible compression of the internal carotid arteries were also reported. Here, we introduced the treatment and prognosis (especially the operation) in detail, which is lacking in most cases. More importantly, we used the ENS in PS patients, which is unstated in previous reports. The overgrowth of the optic canal results in confinement of the orbital apex area of the patient with serious consequences. Therefore, an accurate location is of extreme importance, and ENS works as the key technique here. Based on a normal endoscopic surgery system, ENS is highly safe, minimally invasive, causes minimal tissue loss, and allows direct observation of the optic nerve[17]. Together, infrared confirming orientation technology helps to further lessen the error[18]. These techniques help us to position the operative region depending on the preoperative design[19] and achieve precision surgery (Figure 2C 1st and 2nd line).

Here, we review the literature on Proteus syndrome cases with ocular manifestations. Available English literature was collected in the MEDLINE (OVID), Embase, and Web of Science databases until November 2022. The keywords were: Proteus syndrome AND ophthalmology; Proteus syndrome AND orbit; Proteus syndrome AND ocular; Proteus syndrome AND eye; and Proteus syndrome AND case. Notably, we diagnosed cases using the latest criteria[4,15] and summarized the clinical features and ocular manifestations of diagnosed PS cases (**Supplementary Table I**).

We summarized 48 cases with ocular features and found that both sexes were approximately equal, and most ocular manifestations were unilateral. Proptosis, strabismus, myopia, and retinal abnormalities were the most common nondiagnostic criteria. Although ocular features were recorded in many cases, ophthalmic treatment and prognosis were rarely recorded, and none of the patients died from ocular symptoms. Therefore, we strongly recommended diagnosing ocular features with specific ophthalmic examinations and referring patients to the Department of Ophthalmology for specialty treatment.

As only approximately 200 PS cases have been reported to date, the diagnostic criteria of PS are mostly based on clinical findings with all general and adequate specific criteria as follows. Molecular genetic testing of AKT1 would help to diagnose PS[4].

- general criteria: mosaic distribution of lesions, sporadic occurrence, and progressive course.
- specific criteria: 1 from category A, 2 from category B, or 3 from category C (Table I).

This case was diagnosed as PS based on general criteria: the linear epidermal nevus on the patient's back and thighs; the overgrowth of her limbs, skull, and external auditory canal; the presence of megaspondylodysplasia (Figure 1). The ophthalmic differential diagnoses mainly include neurofibromatosis, which is highly likely to result in visual decline at an early age[20]. Other diseases in the differential diagnosis are PTEN hamartoma tumor syndrome, CLOVE(S) syndrome, hemihyperplasia, Klippel-Trenaunay syndrome, and Bannayan-Riley-Ruvolcaba syndrome[4,21,22].

Identification of a somatic mutation of AKT1 by molecular genetic testing is helpful for early diagnosis, especially when the clinical criteria are inconclusive[4]. It is commonly agreed that

Table I. Specific criteria for Proteus Syndrome*.

Category signs	Manifestations
A	Cerebriform connective tissue nevus
B	Linear epidermal nevus
	Asymmetric, disproportionate overgrowth (≥ 1):
	Limbs
	Hyperostosis of the skull
	Hyperostosis of the external auditory canal
	Megaspondylodysplasia (i.e., abnormal growth of vertebrae)
	Viscera: spleen/thymus
	Specific tumours with onset before 20 (≥ 1):
	Bilateral ovarian cystadenoma
	Parotid monomorphic adenoma
C	Dysregulated adipose tissue (≥ 1):
	Lipomatous overgrowth
	Regional lipoatrophy
	Vascular malformations (≥ 1):
	Capillary malformation
	Venous malformation
	Lymphatic malformation
	Bullous pulmonary degeneration;
	Facial phenotype (all):
	Dolichocephaly
	Long face
	Downward-slanting palpebral fissures and/or minor ptosis
	Depressed nasal bridge
	Wide or anteverted nares
	Open mouth at rest

*Based on Biesecker et al[4].

PS is mainly caused by somatic mosaicism activating mutations of AKT1 (mostly c.49G>A, p. Glu17Lys) or abnormal activation of the PI3K-AKT pathway[8]. Ubiquitous expression of mutated AKT1 results in embryonic lethality[23], and alterations in PTEN in PS are still under discussion[24,25]. This typical mutation provides new thinking for PS treatment. The effect of AKT1 variants on the vascular endothelium leads to a higher risk of thrombosis in PS patients and highlights the surveillance of thrombosis after surgery[26]. Activating mutations in AKT1 have also been identified in a variety of cancers, such as breast cancer, colorectal cancer, and prostate cancer[27-29]. AKT1 increases cell proliferation in these cancers, which is partly similar to its function in PS[30,31]. Therefore, similar to some oncotherapies, AKT inhibitors function in PS treatment and show great therapeutic potential in personalized medicine[32].

Limitations

The novel ophthalmologic surgical procedures were applied with partial success here, and there are limitations that require further follow-up: a genetic analysis was not performed to confirm the diagnosis, the progress of the disease was continuous after a series of treatments, and a lifetime follow-up should be scheduled reasonably. As hyperostosis is one of the characteristics of our patient, osteotomy, such as that involving her face and limbs, was performed several times because of recidivation. Therefore, a longer-term, even lifetime, follow-up is necessary. We have already found regrowth of the medial orbital wall and recompression of the optic nerve and ICA at the latest follow-up. It indicated that further surgeries should be arranged when the disease develops during the follow-up phase, and a genetic analysis needs to be carried out at that time.

Conclusions

In summary, PS is an extremely rare and highly variable disease with multiple system and organ disorders. Here, we described a patient with ocular symptoms who benefited from an endoscope-navigation system aided by optic canal decompression. Therefore, we emphasize

coherent, comprehensive treatments and combined surgeries by a multidisciplinary team. In addition, disfigurement for some individuals may cause psychosocial issues for many families. Exploring novel and minimally invasive methods with smaller and more sheltered scars is a higher requirement.

Conflict of Interest
The authors declare that they have no conflict of interests.

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Ethics Approval
Not applicable.

Informed Consent
The guardian of the patient signed informed consent before the procedure.

Authors' Contribution
YW and RJ conceived and designed the work. RJ undertook the acquisition and analysis of the data. All authors contributed to the interpretation of the data. RJ drafted the work, with all other authors revising and/or critically evaluating it for intellectual content.

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