The pathogenesis of TCS was initially thought to be due to defective ossification of the facial bones. However, the common derivation of the affected tissues from the first and second branchial arches led to speculation that defects in neural crest cell migration might be responsible. More recently, it has been suggested that premature cell death in the ectodermal placodes of the first and second branchial arches, rather than impaired migration of neural crest cells, may instead be the pathogenetic mechanism.

The gene responsible for TCS has recently been cloned, and a protein product has been identified with homology to a family of nucleolar-cytoplasmic transport proteins. Almost all mutations identified in TCS result in premature termination of the protein product, suggesting that the pathogenetic effects result from haploinsufficiency of the gene product during embryogenesis. The precise function of this protein product and its role in TCS pathogenesis remain unknown. As a result of this research, a genetic test for prenatal diagnosis in affected families is now available.

Of note, the prevalence of cataracts is variable in other craniofacial syndromes involving malformation of the first and second branchial arches. They are seen very frequently in Hallerman-Streiff syndrome, occasionally in Pierre Robin syndrome, and are absent in Goldenhar syndrome.

Though the literature refers to cataract as an infrequent ophthalmic finding in TCS, no specific cases with cataract could be identified. There were no cataracts mentioned in 2 recent case series that examined the ocular findings in 14 and 24 patients with TCS, respectively.

To our knowledge, this is the first reported case of delayed-onset infantile cataracts in TCS. It is significant because this child displayed no signs of cataract at birth or at 10 months of age but developed bilateral, visually significant cataracts by 13 months of age. The possibility that delayed-onset cataracts can develop rapidly in infants with TCS suggests that more frequent ophthalmologic follow-up and detailed anticipatory guidance to parents are warranted to prevent the possibility of undetected cataracts leading to irreversible amblyopia.

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Vesicular Erup tion in a Child With Trigeminal Nerve Palsy During Topical Therapy With Substance P and Insulinlike Growth Factor I for Neurotrophic Keratitis

In 1997, Brown et al reported on the use of substance P and insulin-like growth factor I for the topical treatment of neurotrophic and anhidrotic keratitis in a child. Since then, other authors have used these compounds2-3 to treat a variety of corneal conditions that caused chronic focal or diffuse epithelial disruption. Herein, we report a possible complication when the combination of substance P and insulinlike growth factor I was used to treat neurotrophic keratitis in a child with complete trigeminal nerve (cranial nerve V) palsy.

Report of a Case. A 28-month-old girl sustained permanent, total left trigeminal nerve palsy after a motor vehicle crash. She was referred to us 3 months later with a chronically red eye and partial ptosis. The mother reported that the child would vigorously rub and pick at her left nostril (causing bleeding), scratch her cheek, and also dig her fingers into her left inferior conjunctival fornix, without evidence of pain. On examination, the inferior conjunctiva was diffusely injected. The exposed inferior third of the cornea was rough and partly opaque, with adherent mucous strands. The cornea underneath the pteryotic lid was clear and lustrous. Partial oculomotor nerve palsy prevented an adequate Bell reflex. Lacrimation could not be tested, but an adequate, although mucoid, tear lake was present. Formal testing of corneal and periciliar sensation was not attempted. The diagnosis was traumatic, neurotrophic, and exposure keratopathy. Initial treatment with heavy topical lubrication and erythromycin ointment failed to prevent frequent recurrent erosions and superimposed bacterial keratitis. A lateral tarsorrhaphy was performed, but the cornea failed to stabilize, partly because of the child’s self-mutilating behavior.

On the basis of our previous experience, we elected to treat the child with substance P (Multiple Peptide Systems, Inc, San Diego, Calif), 250 µg/mL, combined with insulinlike growth factor 1 (Boehringer-Mannheim GmbH, Mannheim, Germany), 25 ng/mL, dissolved in hyaluronate sodium (Healon GV; Pharmacia & Upjohn, Inc, Kalama-zoo, Mich), 1 drop 3 times daily. Investigational drug approval was obtained from the US Food and Drug Administration. The first scheduled follow-up visit at 1 week was not completed. The child was seen 2 weeks after initiating treatment. Her mother reported that after 2 to 3 days, she developed white blisters along the lower eyelid margin, and redness and blistering of the lower lid and the cheek. The mother discontinued the medication after 7 days of treatment. The lid margin blisters resolved rapidly.

Seven days after discontinuation, the inferior conjunctiva was somewhat less injected than before
treatment. The chronic inferior corneal erosion had partly reepithelialized at its nasal and temporal corners. The lid margins were normal. The Figure shows the left lower eyelid and the skin of the cheek.

Comment. To the best of our knowledge, this is the first reported case in which a combination of substance P and insulinlike growth factor I was used to treat neurotrophic keratitis in a patient who also had trigeminal trophic syndrome. Trigeminal trophic syndrome occurs in patients with facial paresthesias due to trigeminal nerve injury. As in this child, compulsive nose picking is a typical feature. Our patient had a mild manifestation of this syndrome, which often can result in complete loss of the nasal ala due to persistent self-mutilation. After several days of topical ophthalmic administration of the substance P–insulinlike growth factor I combination, the mother observed a blistering or vesicular reaction involving the lower eyelid margin and surrounding skin, which began to resolve when the medication was discontinued. We have treated 2 previous children with a combination of substance P and insulinlike growth factor I, both with congenital corneal anesthesia alone, who did not develop a cutaneous reaction during many weeks of therapy.

There are several possible explanations for the vesicular eruption seen in our patient. First, a substance P agonist has been shown to mediate contact hypersensitivity in the skin. Both irritant contact dermatitis and allergic contact dermatitis have been shown to be enhanced by neuropeptides, including substance P. Contact hypersensitivity may have occurred when up-regulated cutaneous substance P receptors were suddenly exposed to normal or supra-normal levels of substance P. Irritant contact dermatitis and allergic contact dermatitis can be seen as vesicles in the acute stages of the eruption. Second, the vesicular eruption could have been a herpetic infection (probably due to herpes simplex virus 1). The latter may have occurred coincidentally or may have been stimulated by the substance P–insulinlike growth factor I combination therapy. No previous causal relationship between substance P–insulinlike growth factor I combination therapy and herpetic infections has been reported. Because the initial clinical impression was that this was a resolving dermatitis, viral cultures from the cheek ulcer were not obtained. Finally, we used the hyaluronic acid–insulinlike growth factor I combination as the drug vehicle to increase surface retention and decrease the dosing frequency to 3 times per day. In the previously reported case, we used balanced salt solution with a dosing frequency of 1 drop every 15 minutes for 2 hours, twice a day. It is remotely possible that this case represents an allergic contact dermatitis to the hyaluronate vehicle.

Substance P combined with insulinlike growth factor I topical therapy has not been performed. Substance P with insulinlike growth factor I has proved effective in several cases of chronic neurotrophic keratitis unresponsive to customary therapies. Patients with trigeminal trophic syndrome, atopic dermatitis, or other types of allergic skin disease may have a cutaneous blistering reaction to these agents when applied to the surface of the eye. Increased contact hypersensitivity due to substance P is one possible mechanism. Physicians should be alert to this possibility when substance P (with or without insulinlike growth factor I) is used to treat recalcitrant neurotrophic keratitis in patients who have periorbital cutaneous denervation.

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