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ORIGINAL ARTICLES

Photic sneeze reflex in nephropathic cystinosis*

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Abstract

Photic induced sneeze is a reflex that occurs in certain individuals after exposure to bright light. Cystinosis is an autosomal recessive inborn error of metabolism in which non-protein cystine accumulates within lysosomes. The pathognomonic ocular manifestation of cystinosis is corneal crystal deposition. We observed photic induced sneezes during ophthalmoscopic examination in five of 19 patients with nephropathic cystinosis (26%). We report on this observation and discuss possible pathophysiological mechanisms for photic induced sneezing in cystinosis.

Sneezing in response to bright light is a peculiar phenomenon that may occur in otherwise normal people.[1] It most commonly occurs as a subject walks outside into bright sunlight; on occasion it happens during ophthalmoscopy and rarely with slit-lamp illumination. While numerous investigators have commented on this unique reflex,[2-4] its physiological mechanism has not been clearly defined.

Cystinosis is an autosomal recessive metabolic disorder in which non-protein cystine accumulates in most body organs.[5] The cystine accumulates within the lysosomes of cells owing to a defect in lysosomal cystine transport.[6] Cystinosis is divided into two major clinical groups, nephropathic and benign. Systemic complications of the former include the renal Fanconi syndrome with rickets and growth retardation, and glomerular failure necessitating renal transplantation by an average age of 10 years. All phenotypes of cystinosis are associated with ocular manifestations. The pathognomonic ocular manifestation of cystinosis is the presence of distinctive iridescent crystals within the conjunctiva and cornea. Histologically the crystals are birefringent, intracellular, and of varying morphology.

Crystals have also been seen in the iris, ciliary body, choroid, retinal pigment epithelium, sclera, episclera, extraocular muscles, and optic nerve sheath.[7-9] A pigmentary retinopathy characteristically affecting the periphery has been described in the nephropathic form of the disease,[10] though not observed in the benign form.[11] Although cystine crystals may be deposited in the choroid plexus and on rare occasion are seen within brain parenchyma,[12] patients with cystinosis have been thought to be neurologically normal. Recent work has suggested that these patients do have neurological dysfunction.[13,14] While cystinosis affects many ocular structures, the only complaints of patients are, generally, photophobia and glare.

In the course of our on-going study of the neuro-ophthalmological manifestations of nephropathic cystinosis we observed photic induced sneeze in a disproportionate number of these patients. We report on this observation, and relate its occurrence in cystinosis to a possible underlying pathophysiology.

Patients and methods

We examined 19 patients with the infantile-onset form of nephropathic cystinosis. All had photophobia, though none had excessive lacrimation or obvious nasal allergies. All patients had normal visual acuity with normal colour vision (pseudoisochromatic plates). Their pupillary responses were normal, without evidence of afferent pupillary defect. No sectoral abnormality of iris innervation was noted, and accommodation was normal for age. Corneal reflexes were clinically normal in all the patients, and trigeminal function was intact. On four of the 19 we performed electrophysiological blink reflex studies, with transcutaneous stimulation of the supraorbital nerve and surface recording of the orbicularis oculi motor action potential. In all patients so studied a normal afferent limb to the blink reflex was demonstrated.

All of the cystinosis patients had extensive crystal deposition in the conjunctiva and cornea. Ophthalmoscopy revealed all patients to have depigmentation of the peripheral retina, with a patchy, mottled appearance to each fundus from the mid equator to the ora serrata. Optic nerves were of normal colour, contour, and capillarity. No defect of nerve fibre layer could be detected.

Results

During the course of slit-lamp biomicroscopy two of the 19 patients had a photic induced sneeze, and during indirect ophthalmoscopy three more patients had one. Thus five of 19 (26%) nephropathic cystinosis patients showed this reflex. The sneeze occurred at the beginning of the exposure of the retina to light and did not persist with continued exposure. Pupillary evaluation with a hand held muscle light before slit-lamp examination and indirect opthalmoscopy did not precipitate a photic sneeze in any patient. Of 100 control patients prospectively examined in the same manner none sneezed in

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response to the light of the indirect ophthalmoscope or slit-lamp.

Discussion

Collie *et al* characterised the photic induced sneeze as an uncontrollable paroxysm of sneezing provoked in a reflex fashion by the sudden exposure of a dark-adapted subject to intensely bright light.[15] The reported incidence of the photic sneeze reflex is surprisingly high. Peroutka and Peroutka reported it to be present in nine of 25 neurologists (36%), though their data were derived from questionnaires.[16] Everett[1] reported a history of photic sneeze in 68 of 414 persons (16·4%) surveyed. He found a higher incidence in Caucasians than blacks, and in those who had noted the reflex in family members, and he concluded that heredity was a factor in predisposing to photic sneeze. In a study of four families Collie *et al* found a distribution consistent with an autosomal dominant inheritance pattern for the trait, with a high degree of penetrance.[15]

The usual source of stimulation in susceptible people is sunlight, though artificial light may also precipitate a sneeze. Sedan described the reflex in patients exposed to such varying stimuli as the indirect ophthalmoscope, photographic flash, and ultraviolet light.[17] Although generally harmless, photic induced sneezing has been reported to cause conduction deafness, mediastinorrhexis, and cerebral haemorrhage.[15] Moreover, the photic sneeze reflex may be more than just a curiosity to those whose work requires exposure to flashes of illumination.[15]

Sedan[17] and Everett[1] noted a feature seen also in the current study, namely that the sneezing occurred at the beginning of the exposure of the retina to bright light but did not persist with continued exposure or when the exposure was soon repeated. The stimulating light seems to precipitate the reflex when it follows a period of relative darkness. Elicitation of the reflex produces a latency interval during which the retina is refractory to further photic induced sneezing.

What does the prevalence of photic sneeze in cystinotic patients say about the underlying pathophysiology of this reflex? Our patients with nephropathic cystinosis all had corneal infiltration with cystine crystals. The occurrence of this reflex in the setting of corneal dysfunction has been recognised previously,[3] and keratitis has been reported to enhance the photic sneeze reflex.[17 18] Lewkonia described a man with corneal oedema and vascularisation following alkali burn.[3] The patient sneezed during ophthalmoscopic and slit-lamp examination. He was seen daily for his keratopathy, and the progression of his photic sneeze was recorded. The occurrence of sneeze reflex decreased as the cornea healed. Keratopathy, however, is neither a necessary nor sufficient criterion for photic sneeze.

Another hypothesis for photic induced sneeze reflex invokes optic-trigeminal summation.[1] Eckhardt *et al* postulated that stimulation of the optic nerve enhances the irritability of the trigeminal nerve.[19] Photic stimuli may produce referred sensation in fibres carried by the first division of the trigeminal nerve.[19] Such summation may involve the second division of the trigeminal, thus enhancing nasal stimulation to the point of precipitating the sneeze synkinesis.[1] Wirtschafter and Bourassa concluded that trigeminal nerve stimulation may greatly increase sensitivity to light.[20] Such interactions could explain the photophobia observed in patients with cystinosis.

The cystinotic patient may have an underlying irritability of the trigeminal nerve related to crystal deposition in the cornea. The peripheral branches of the trigeminal nerve behave abnormally in cystinosis.[21] This is postulated to be secondary to altered function in the basal epithelial neural plexus and penetrating anterior corneal nerves or their end organs, corresponding to the recognised site of maximal cystine crystal deposition.[21 22] Peripheral trigeminal dysfunction may incite an alteration in more central control mechanisms, culminating in trigeminal supersensitivity and susceptibility to ephaptic transmission. The trigeminal nerve may become especially sensitive to both stimulus generalisation and stimulus summation. Watson stated that the photic sneeze 'occurs most frequently when there is a morbid sensitiveness [of] ... the fifth [nerve] ... centrally reflected to the retina.'[18] Light falling on the retina stimulates afferent fibres to the pretectal nuclei, which then send interneurons to the Edinger-Westphal nuclei. The parasympathetic fibres from the Edinger-Westphal nuclei and the trigeminal afferent fibres from the cornea both pass through the ciliary ganglion, where they may participate in ephaptic transmission.

Parasympathetic generalisation may contribute to photic sneeze. Stimuli which excite primarily one branch of the parasympathetic nervous system tend to activate other branches.[1] Light falling on the retina stimulates pupillary contraction, subserved by parasympathetic fibres of the oculomotor nerve. The parasympathetic activity of miosis may produce congestion of and secretion from the nasal mucosa (mediated through the seventh nerve and the sphenopalatine ganglion), factors which are recognised to initiate sneezing.[23]

In summary, the photic induced sneeze is a reflex which seems to involve diverse neuroanatomical substrates including the optic, oculomotor, and trigeminal nerves, autonomic pathways, and central brainstem structures. Its remarkable prevalence in a nephropathic cystinosis population offers an opportunity for further study of its underlying pathophysiological mechanisms.

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1 Everett HC. Sneezing in response to light. *Neurology* 1964; **14**: 483–90.
2 Kofman O. Paroxysmal sneezing. *Can Med Assoc J* 1964; **91**: 154–7.
3 Lewkonia I. An infrequent response to slit lamp examination. *Br J Ophthalmol* 1969; **53**: 493–5.
4 Everett HC. Reply to Pratt AG. Photic sneezing [Letter]. *JAMA* 1965; **191**: 153–4.
5 Schneider JA, Schulman JD. Cystinosis. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. *The metabolic basis of inherited disease*. New York: McGraw-Hill, 1983: 1844–66.
6 Jonas AJ, Smith MD, Schneider JA. ATP-dependent lysosomal cystine efflux is defective in cystinosis. *J Biol Chem* 1982; **257**: 13185–8.

7 François J, Hanssens M, Coppieters R, Evens L. Cystinosis: a clinical and histopathologic study. *Am J Ophthalmol* 1972; **73**: 643–50.
8 Sanderson PO, Kuwabara T, Stark W, Wong VG, Collins EM. Cystinosis: a clinical, histopathologic and ultrastructural study. *Arch Ophthalmol* 1974; **91**: 270–4.
9 Frazier PD, Wong VG. Cystinosis: histologic and crystallographic examination of crystals in eye tissues. *Arch Ophthalmol* 1968; **80**: 87–91.
10 Wong VG, Lietman PS, Seegmiller JE. Alterations of pigment epithelium in cystinosis. *Arch Ophthalmol* 1967; **77**: 361–9.
11 Lietman PS, Frazier PD, Wong VG, Shotton D, Seegmiller JE. Adult cystinosis – a benign disorder. *Am J Med* 1966; **40**: 511–7.
12 Ross DL, Strife CF, Towbin R, Bove KE. Nonabsorptive hydrocephalus associated with nephropathic cystinosis. *Neurology* 1982; **32**: 1330–4.
13 Trauner DA, Chase CH, Scheller JM, Katz B, Schneider JA. Neurologic and cognitive deficits in children with cystinosis. *J Pediatr* 1988; **112**: 912–4.
14 Katz B, Melles RB, Trauner DA, Schneider JA. Saccadic abnormalities in nephropathic cystinosis. *J Clin Neuro Ophthalmol* 1988; **8**: 115–9.
15 Collie WR, Pagon RA, Hall JG, Shokeir MHK. ACHOO syndrome (Autosomal Dominant Compelling Helio-Ophthalmic Outburst syndrome). *Birth Defects* 1978; **14**: 361–3.
16 Peroutka SJ, Peroutka LA. Autosomal dominant transmission of the 'photic sneeze reflex.' *N Engl J Med* 1984; **310**: 599–600.
17 Sedan J. Reflexe photo-sternutatoire [photo-sternuatatory reflex]. *Rev Oto-neuro-ophtal* 1954; **26**: 123–6.
18 Watson WS. *Diseases of the nose and its accessory cavities.* London: Lewis, 1875: 343.
19 Eckhardt LB, McLean JM, Goodell H. The genesis of pain from the eye. *Assoc Res Nerv Mental Dis Proc* 1943; **23**: 209–7.
20 Wirtschafter JD, Bourassa CM. Binocular facilitation of discomfort with high luminances. *Arch Ophthalmol* 1966; **75**: 683–8.
21 Katz B, Melles RB, Schneider JA. Corneal sensitivity in nephropathic cystinosis. *Am J Ophthalmol* 1987; **104**: 413–6.
22 Melles RB, Schneider JA, Rao NA, Katz B. Nephropathic cystinosis: spatial and temporal sequence of corneal crystal deposition. *Invest Ophthalmol Vis Sci* 1987; **28** (suppl): 222.
23 Brubaker AP. The physiology of sneezing. *JAMA* 1919; **73**: 585–7.