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Hypothesis: Patient with Possible Disturbance in Programmed Cell Death

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Abstract
Programmed cell death is a physiological process in mammalian development by which specific types of cells are eliminated, and, hence, is of fundamental importance in normal human embryogenesis. A patient is described with multiple congenital anomalies that may be explained by a disturbance of programmed cell death. Anomalies included macrocephaly, hypoplastic lacrimal ducts, narrow external ear canals, pharyngeal mucous membrane fold, unilateral cryptorchidism, cord-like vasa deferentia, and complete cutaneous syndactyly of the hands and feet.

Les morts gouvernent les vivants.
Auguste Comte (1852)

Introduction

In most organisms, normal embryogenesis is not only dependent on mitosis and cell differentiation, but also on cell death. Cell death can occur when cells deviate strongly from normal developmental pathways, for instance during severe hyperthermia, hypoxia, or ischemia. This type of cell death is known as necrosis. Cell death also occurs in physiological development, i.e. in the absence of obvious external insults, when cells are deliberately eliminated in a morphologically distinct manner. This programmed cell death is referred to as apoptosis [1]. Its occurrence in normal embryogenesis is widespread [2, 3].

Here, were report on an adult male with multiple congenital anomalies that may be explained as consequences of disturbed embryonic programmed cell death.

Case Report

The propositus, the product of a normal pregnancy and delivery, was the first child of healthy, nonconsanguineous parents. His sister was normal. His paternal grandfather's sister was said to have had an 'attached upper lip' (maxillary alveolar frenulum?), and a grandson of a brother of the paternal grandfather was said to have 'his tongue attached to his palate' (ankyloglossum superior?). No further information was available.

Anomalies of the face and limbs, as well as extremely narrow auditory canals were noted immediately after birth. In the neonatal period, respiratory problems were present that persisted, requiring eventual tracheostomy at 8 months of age. During that procedure, a large fold of mucous membrane above the vocal cords was detected.

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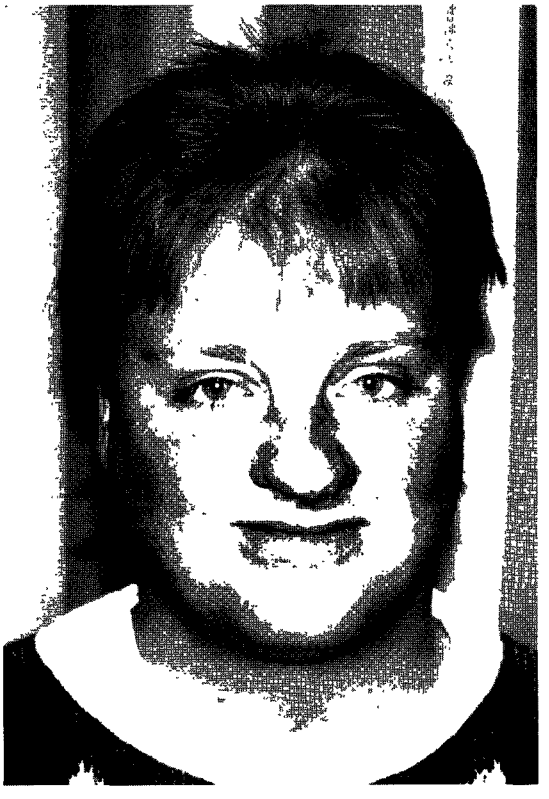

Fig. 1. Propositus at 28 years of age. Note hypertelorism, short palpebral fissures, broad nasal root, full nasal tip, hypoplasia of the premaxilla, prominent lips, and relative prognathism.

Fig. 2. The feet of the propositus. Note the resemblance to the syndactyly found in Fraser syndrome.

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Several surgical interventions were performed in the following years, including a procedure for hypoplastic lacrimal ducts, widening of the auditory canals, correction of unilateral cryptorchidism, repair of the cutaneous manual syndactyly, and termination of the tracheostomy at 6 years of age. During childhood he suffered from repeated and prolonged periods of bilateral otitis media that persisted into adulthood. Cholesteatomas had to be removed frequently.

On physical examination (fig. 1) at 28 years of age, head circumference was 59.1 cm (>98th centile), intelligence was normal, height was 1.79 cm (25–50th centile). He had somewhat sparsely implanted hair, brachycephaly, hypertelorism and narrow palpebral fissures (inner canthal distance 3.6 cm, >98th centile; outer canthal distance 8.9 cm, 60th centile), a broad nasal root, full nasal tip, hypoplastic premaxilla, short philtrum, prominent lips, small teeth, and relative mandibular prognathism. Despite earlier surgery, his auditory canals were still narrow. Some residual manual syndactyly also persisted. There was moderate camptodactyly, and short, slightly abducted thumbs. Fingernails were normal, but toenails were very small. He had complete cutaneous syndactyly of all toes (fig. 2).

A radiographic skeletal survey was normal. An orthopantomogram demonstrated microdontia (fig. 3). Magnetic resonance imaging (MRI) of the brain showed a normal grey matter/white matter ratio and no anatomical anomalies. The Eustachian tube could not be visualized on MRI, which may indicate hypoplasia. Ophthalmological investigations gave normal results. Visual and acoustic brainstem evoked potentials showed

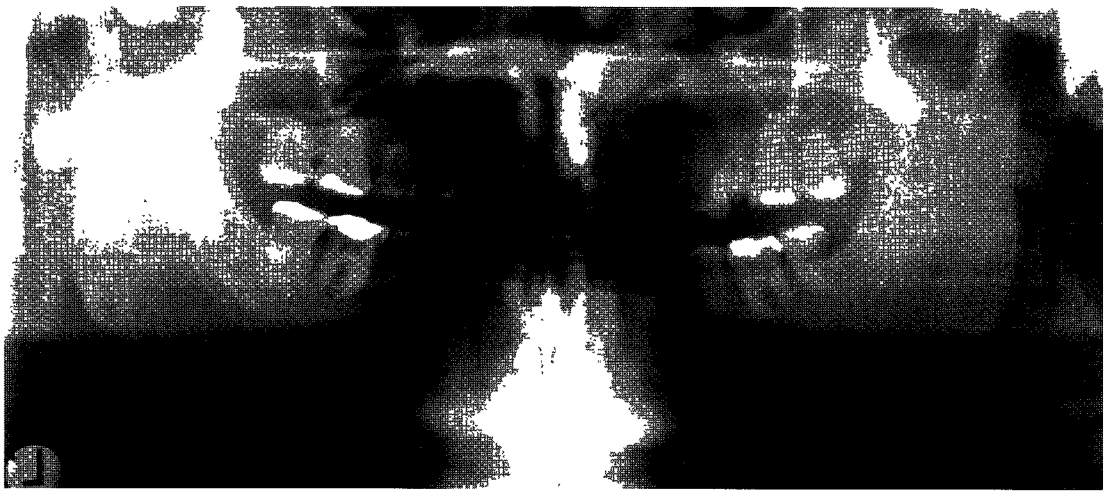

Fig. 3. Orthopantomography showing microdontia.

normal curves. Audiometry showed a mixed hearing loss (20–40 dB). Chromosomes were normal in the patient and his parents. Semen analysis showed azoospermia, and surgical exploration showed bilateral hypoplasia of the epididymis, cord-like vasa deferentia without a lumen, and normal spermatogenesis on testicular biopsy. Molecular studies made cystic fibrosis unlikely.

Discussion

The findings in the present patient do not fit any of the known syndromes. The manifestations are at variance with the Fraser cryptophthalmos syndrome [4, 5], despite some similarities. It has been suggested that mouse 'bleb' mutants provide a model for Fraser syndrome [6, 7], but others have suggested deficient programmed cell death of neural crest cells as a cause [8]. Both models would explain the features of our patient, who has a more generalized disturbance of apoptosis.

Programmed cell death is known to occur at different times during normal embryonic and fetal life as well as postnatally [9–11]. Several authors have performed careful analyses of apoptosis in human and other vertebrate embryos and fetuses [2, 3] to establish when and where programmed cell death takes place. The anomalies present in our patient occur in areas subject to prenatal programmed cell death: ear canals, lacrimal ducts, buccopharyngeal membrane, webs between the fingers and toes, and vasa deferentia. Even macrocephaly can result from disturbed cell death; only a small proportion of the developing brain escapes significant prenatal degeneration [12]. The mean proportion of brain cell loss has been estimated to be as high as 40%. No firm explanations are as yet available for the facial features, including the microdontia.

Apoptosis is thought to be influenced by many factors, such as hormones, cell-to-cell interactions, and intracellular proteolytic systems [1, 9, 13]. However, apoptosis is also a gene-directed process. This has been particularly well studied in the nematode *Caenorhabditis elegans* [14] and in *Drosophila* [15]. It seems probable that some genes are involved in all programmed cell death and others in particular forms of cell death. In our patient, it remains uncertain whether a faulty gene-directed process has been the primary cause or whether programmed cell death has been temporarily influenced by some exogeneous cause. Because of the absence of obvious postnatal disturbances in apoptotic processes in the propositus, either a disturbed particular form of programmed cell death or a temporarily disturbed, more general form seems most probable. This may also explain why other anomalies are not present.

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