Letter to the Editor

SOX2 anophthalmia syndrome – a neurodegenerative picture?

To the Editor:
Heterozygous, loss of function mutations in the high mobility group (HMG) gene, SOX2, encoding the sex-determining region Y-box 2 (MIM 184429) protein, lead to severe developmental eye and brain malformations, and some anophthalmos-esophageal-genital syndrome cases (1). However, the fate of these cases into adulthood is unknown. We report an adult with SOX2 anophthalmia syndrome who is exhibiting features suggesting neurodegeneration.

A 35-year-old male with bilateral anophthalmia was referred for genetic diagnosis. He was the third son born at term to unrelated parents (mother 25 years, father 32 years), weighing 6lb 9oz. Post-delivery, he developed peripheral cyanosis and was diagnosed with bilateral anophthalmia on admission to intensive care.

In early childhood, he suffered recurrent infections and poor feeding with persistent choking episodes. He had delayed motor development, sitting at 17 months, walking at 3.5–4 years. He developed an atypical seizure disorder, treated with valproate. He had a duplex kidney and ureteric reflux, with recurrent infections. His speech and language development was delayed: at 3 years, he spoke ~30 words, losing some by 4 years. By 10 years his language, motor and social development had not significantly progressed. Puberty occurred normally. His brother had mild sensorineural deafness; there was no other relevant family history.

Over recent years, his condition deteriorated. He lost speech and experienced increased difficulties with walking and swallowing, premature graying, occasional drop attacks and cyanotic episodes of unknown aetiology. His electrophysiology and echocardiography were normal. His electroencephalography at 31 years showed some frontotemporal sharp and slow waves, but not diagnostic of epilepsy. His kidney function was reduced on imaging with Tc-99m-mercaptoacetyltriglycine (MAG 3) scan (right 33%; left 67%). Post-delivery, he developed peripheral cyanosis and was diagnosed with bilateral anophthalmia on admission to intensive care.

His examination showed bilateral anophthalmia, short palpebral apertures, underdeveloped orbital bones, slightly square earlobes and underdeveloped helices (Fig. 1a,b). His head circumference was 56 cm (25–50%). He had spastic diplegia, and fatigued easily.

His magnetic resonance imaging scan at 31 years showed prominent cerebrospinal fluid spaces and ventricles, consistent with global loss of brain volume (Fig. 1c–e). Since there are no other scans for comparison, the timeframe for the change is unknown. There were non-specific scattered areas of increased T2 signal intensity within predominantly frontal subcortical white matter. These are of unknown clinical significance and do not resemble heterotopia. The pituitary fossa was present and anterior pituitary tissue was identifiable. Hippocampal volume was reduced bilaterally.

Molecular analysis of the SOX2 gene revealed a de novo mutation c. 181C>T p.Gln61X in the HMG DNA-binding domain predicted to lead to haploinsufficiency of SOX2. This mutation has been reported in another case (2).

Our patient had typical SOX2 syndrome with bilateral anophthalmia, seizure disorder, spastic diplegia, pervasive neurodevelopmental disorder, renal anomalies and swallowing difficulties (1). Brain malformations are frequent in SOX2 cases, mainly hypothalamic-pituitary anomalies, corpus callosal agenesis or hippocampal malformations, occasionally, hydrocephalus and deafness (2). Our patient’s white matter lesions have not been reported before. It is unclear if they relate to his neurological decline.

Although most SOX2 cases exhibit severe phenotypes with major eye anomalies, phenotypic variability is emerging; some individuals even have normal or minimally affected eyes (3). Contributing factors include genetic background, mutation type, local and stochastic factors. Since SOX2 belongs to a close family of SOX genes, there may be genetic redundancy within the group. Sox2 paralogues of the Sox B1 subgroup, Sox1 or Sox3, can rescue Sox2 deficiency in animal models. The mutation type may be important: a four-generation family with varying ocular phenotypes has been reported with a SOX2 missense mutation within the partner factor-binding domain, not involving the HMG domain (3). Although the overwhelming majority of SOX2 cases are de novo and severe, phenotypic variability and occasional mosaicism suggest caution when advising family members about recurrence risk. Here, it would be sensible to screen our patient’s brother, whose only symptom is deafness.

There is evidence supporting a generalized role for Sox2 in both neurogenesis and neuropreservation from mouse models of central nervous system (CNS) development (4). Compound heterozygous mouse embryos with markedly reduced Sox2 expression display decreased hippocampal and subventricular neurogenesis analogous to hippocampal and periventricular abnormalities seen in SOX2 cases. SOX2
individuals often exhibit a motor planning disorder, possibly comparable to thalamo-striate defects seen in the mouse model (4). Moreover, Sox2 deficient mice suffer neurodegeneration, to the extent that intracellular inclusions in neurons, and degenerate cells are visible at a relatively young age (4). Although other SOX2 individuals described by this group have reached their twenties (1), we have not learned of any with neurological deterioration to date. Our proband appears to be the oldest SOX2 haploinsufficient (non-mosaic) individual described and may be exhibiting neural decline that may affect others once they reach this age. Significantly, individuals with other eye development conditions (e.g. oculodentodigital dysplasia GJA1) have been noted to exhibit neural decline (5).

As well as neuropreservation, SOX2 may be important in neural regeneration. The B1 subgroup encode proteins with a C-terminus activation domain, whilst the B2 subgroup encode proteins with a repression domain, creating a fine balance between B1-mediated activation and B2-mediated repression of target genes. For example, Sox1-3 are expressed in progenitor cells in developing CNS, where their protein products block neurogenesis by maintaining cells in an undifferentiated state, controlled by B2 proteins (6). Furthermore, Sox2 is considered a marker for stem cells capable of replicating autonomously and replacing damaged or degenerate tissue, a concept currently utilized in the development of regenerative therapies in conditions, such as Huntington disease and deafness.

Our case represents the first adult with typical SOX2 anophthalmia syndrome, who is manifesting neurological decline. As well as patterning and development, SOX2 may play an important role in neuropreservation in humans.

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