INVITED REVIEW

OPHTHALMIC INVOLVEMENT IN THE FETAL ALCOHOL SYNDROME: CLINICAL AND ANIMAL MODEL STUDIES

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Abstract — The fetal alcohol syndrome (FAS) is caused by maternal alcohol misuse during pregnancy and is characterized by pre- and postnatal growth retardation, central nervous system anomalies and a wide spectrum of malformations, the most typical being the craniofacial features. The eye is a sensitive indicator of the adverse effects of environmental agents, and the ocular abnormalities observed in children with FAS indicate that the developing eye is particularly affected by alcohol. The external signs include short palpebral fissures, telecanthus, epicanthus, blepharoptosis, microphthalmos and strabismus. Within the eyes, the signs and symptoms most commonly detected are optic nerve hypoplasia, increased tortuosity of the retinal vessels and impaired vision. Experimental models of FAS, closely reproducing characteristics of human FAS, have contributed to our understanding of the cellular and molecular basis of the action of alcohol in the developing visual system. As there is such a high frequency of eye signs and symptoms in FAS, an ophthalmological examination is important when making the diagnosis, as well as in the management of the disorder. Current knowledge of ophthalmological involvement in FAS in humans is presented, as well as a review of findings using animal models specially designed for studying ocular developmental changes induced by alcohol.

INTRODUCTION

Alcohol consumption has long been known to produce a variety of effects on the developing human. In the 1960s, data were published from France showing a relationship between maternal alcohol misuse and damage to the fetus (Lamache, 1967; Lemoine et al., 1968). A major event in alcohol research was the description of a distinct dysmorphic condition associated with maternal alcoholism, which was named the fetal alcohol syndrome (FAS) (Jones and Smith, 1973). Affected children display pre- and/or postnatal growth deficiency, central nervous system (CNS) manifestations and major and minor congenital malformations, the most apparent being the craniofacial anomalies (Jones and Smith, 1973; Clarren et al., 1978).

In the wide spectrum of adverse effects of alcohol on the developing organism, FAS is the extreme manifestation, while milder degrees are known as fetal alcohol effects (FAE), alcohol-related birth defects (ARBD) or alcohol-related neurodevelopmental disorder (ARND). The severity of the manifestations of prenatal exposure to alcohol depends on the timing of exposure, the amount of alcohol intake by the mother, the genotypic background and other factors that may exert an influence on the developing human.

The frequency of FAS in the Western world has been estimated to 0.97 cases per 1000 live births (Abel, 1995). In a report based on previously published data, the combined rate of FAS and ARND was 9.1 cases per 1000 live births (Sampson et al., 1997), a frequency that was verified in a study from the French Réunion Island (Maillard et al., 1999). The prevalence of FAS and FAE in Japan is less than 1 case per 10 000 live births (Tanaka, 1998), a low level compared with that from the USA and European countries. A high frequency has been found in certain American Indian reservation communities in the USA, with up to 10 cases per 1000 live births (May et al., 1983; May, 1991). The prevalence of FAS/FAE in children living in an Indian community in British Columbia was estimated to be 190 cases per 1000 children (Robinson et al., 1987). May et al. (2000) examined 992 first-grade pupils from schools in a South African community and noted FAS in 40.5 to 46.4 per 1000 children aged 5–9 years, which is the highest FAS rate, to date, in an overall community population.

The eye is a sensitive indicator of prenatal adverse events, and is therefore useful in the investigation of teratogens, both in humans and animal models. In the human eye, even minor anomalies can be identified by direct inspection, and several signs and symptoms examined by simple clinical methods, such as assessment of visual acuity and ophthalmoscopy to identify retinal fundus pathology. As the early stages of eye development are known, ocular birth defects may be studied in terms of critical time periods for the action of a teratogenic agent. In addition, comparative clinical and experimental studies contribute to a better understanding of the action of alcohol on the developing visual system.

In this article, we review some of the current literature on both the ophthalmological of prenatal alcohol exposure of the developing human, and the animal research in this field. Based on previous studies and our personal experience, we present some ophthalmological landmarks that could assist in making the diagnosis of FAS.

HUMAN STUDIES

General features of FAS

The eyes and vision have been shown to be damaged by maternal alcohol misuse during pregnancy (Altman, 1976;
The retinal fundus abnormalities in FAS range from discrete lesions of the optic disc and retinal vessels to severe malformations of both the retina and the optic nerve. The most frequent abnormalities are optic nerve hypoplasia and increased tortuosity of the retinal vessels (Miller et al., 1984; Strömland, 1985; Chan et al., 1991; Hinzpeter et al., 1992). Hypoplasia of the optic nerve head is characterized by subnormal vision and a subnormal number of optic nerve axons, showing morphological signs such as small size, pallor, irregular margins and an abnormal retinal vascular pattern of the optic disk. Optic nerve hypoplasia was found in a group of Swedish children with FAS, and morphometrically assessed by a specially designed method for digital analysis of retinal fundus photographs. The analysis of the results showed that 48% of the optic discs were hypoplastic in these patients (Strömland, 1985). Retinal vessels are not straight in their course on the retinal fundus, displaying slightly curved forms. Increased tortuosity of the retinal vessels, especially of the arteries, was observed in the same group of children, and digital analysis of fundus photographs showed that 49% of the eyes had this vascular anomaly. Some eyes had a combination of hypoplastic optic disks and abnormal vessel tortuosity.

There are serious consequences to the vision of children with FAS. In the Swedish study, more than half of the affected children had visual impairment, which was severe (visual acuity <0.2) in 12% of the cases (Strömland, 1985). Other authors have also reported visual impairment of different degrees (Miller et al., 1981, 1984; Chan et al., 1991; Hinzpeter et al., 1992; Hug et al., 2000). A follow-up study of Swedish children with FAS (Strömland and Hellström, 1996) showed that those who initially had very poor vision continued to be severely visually handicapped, whereas in those children who had moderately impaired vision, the visual acuity remained unchanged or improved slightly during the study period.

Altered visual-evoked potentials (VEP) were detected in three children with FAS by Chan et al. (1991), although the electroretinograms (ERG) performed in the same patients were normal. More recently, Hug et al. (2000) examined 11 children with FAS, ten of whom displayed optic nerve hypoplasia and reduced visual acuity and had abnormal ERG. Although these findings suggest that prenatal exposure to alcohol might induce changes in the retinal function of children, further studies are needed to confirm these results.

Refraction

Refration varies in children suffering from FAS, ranging from severe myopia to moderate hyperopia (Miller, 1981, 1984; Strömland, 1985; Chan et al., 1991; Hinzpeter et al., 1992). Among Swedish children studied with FAS, refractive errors, often consisting of severe myopia, were present in most eyes with poor vision (Strömland, 1985; Strömland and Hellström, 1996). The eyes had pronounced intraocular malformations, which, together with the refractive errors, were responsible for the poor vision. Additional ophthalmological studies have reported similar findings (Miller et al., 1981, 1984; Chan et al., 1991; Hinzpeter et al., 1992).

Eye examination

An eye examination can be of considerable help in making the diagnosis of FAS, as was shown in a group of mildly mentally retarded children (Strömland, 1990). The ophthalmological

Eye abnormalities

Typical periorcular facial features are short horizontal palpebral fissures, teloanathus (increased distance between the medial eye canthi), epicanthus (vertical fold of the skin on the side of the nose), and unilateral or bilateral blepharoptosis (hanging eye lid). Morphometric methods for objective evaluation of facial features were developed by Astley and Clarrren (1995), using conventional photography, and by Strömland et al. (1998, 1999) using a digital range camera technique. Both methods demonstrating the presence of short palpebral fissures and telecanthus in children with FAS.

Strabismus, most often esotropia, is a frequent finding in children with FAS (Miller et al., 1981, 1984; Chan et al., 1991; Hinzpeter et al., 1992; Hug et al., 2000) and was reported in up to 43% of Swedish cases (Strömland, 1985). Strabismus is a non-specific finding in ophthalmology, which can be considered an additional diagnostic sign of adverse alcohol effects only when it appears together with other typical characteristics of FAS.

Children with FAS may show a spectrum of eye abnormalities, ranging from extensive malformations, such as microphthalmus, buphthalmus (enlarged eye), coloboma of the iris and uvea (abnormal closure of choroidal embryonic eye fissure), persistent hyperplastic primary vitreous body or a severely malformed retina, to minor anomalies (Miller et al., 1984; Strömland, 1985; Chan et al., 1991; Hinzpeter et al., 1992). Microphthalmia has been frequently been observed among children with FAS (Strömland, 1985; Chan et al., 1991) and was included in the criteria for a diagnosis of FAS set by the Fetal Alcohol Study Group of the US Research Society on Alcoholism (Rosett, 1980). Some children give the impression of having small eyes, because of their small head and face and short palpebral fissures. Consequently, a small degree of microphthalmia is difficult to ascertain without objective methods, such as ocular axial length measurements with ultrasonography. Eye size in children with FAS has been studied by this method (Hellström et al., 1997) which demonstrated a shorter total axial length, compared with a control group.

Various abnormalities of the anterior segment and media have been described in FAS, such as Peters’ and Axenfeld’s anomaly (defects of cornea, anterior chamber and iris) (Miller et al., 1984; Hinzpeter et al., 1992), microcornea, iris and uveal coloboma, small centered non-reacting pupil (Strömland, 1985), corneal endothelial abnormalities (Carones et al., 1992) and diffuse corneal clouding (Edward et al., 1993). Single cases of glaucoma, cataract and persistent hyperplastic primary vitreous body have also been observed (Miller et al., 1981, 1984; Strömland, 1985; Hinzpeter et al., 1992).
examination disclosed that at least 10% of this group of children suffered from FAS. A standardized examination includes evaluation of the periorcular facial structures, and looking for external signs such as short palpebral fissures, telecanthus, blepharoptosis, epicanthus and strabismus. Visual acuity is measured and the cornea, anterior segments and media are examined by microscopy for the detection of anomalies. Ophthalmoscopy of the retinal fundus is performed, focusing on optic nerve anomalies, especially hypoplasia, and on retinal vessel tortuosity.

ANTIMAL STUDIES

Teratogenicity of ethanol

The first ophthalmological publication of the adverse effects of prenatal ethanol exposure came from Stockard (1910) who analysed the altered development of chicken and fish eyes following ethanol administration. Sixty years later, the description of the FAS (Jones and Smith, 1973) favored the use of animal models, mainly those trying to reproduce the facial abnormalities found in humans. It has been clearly shown in animal studies that ethanol and/or its metabolites (acetaldehyde) are involved in the teratogenic background of the craniofacial FAS manifestations. Several researchers have shown that malformations associated with FAS are caused by the adverse effects of ethanol/acetaldehyde on embryos prior to or during gastrulation and neurulation, inducing small neural plates, abnormal migration of mesodermal cells and craniofacial malformations. Sulik and Johnston (1983) described craniofacial abnormalities and eye developmental changes in mice exposed to ethanol during gastrulation, resembling those of children with FAS. Cook et al. (1987) and Cook and Sulik (1988) reported a pattern of craniofacial dysmorphism and anterior segment anomalies (including the cornea, conjunctiva, anterior chamber, iris and the lens) in mice exposed to an acute ethanol dose during gastrulation. A smaller size of the lens vesicle was suggested as responsible for the microphakia/aphakia. Alterations in the embryonic contact between the primitive cornea and surface ectoderm were suggested as promoters of the corneal opacification and vascularization. Delayed detachment and global developmental abnormalities of the lens vesicle were involved in the abnormal formation of the anterior chamber and in producing anterior synchiae (punctual fusion of iris to cornea), dyscoria (abnormalities of the pupil), and opacity of the cornea and lens. Persistent hyperplastic primary vitreous has also been described in ethanol-exposed embryos. These observations in animal eyes resemble the clinical signs of shallow anterior chamber, glaucoma, iris coloboma, corneal dystrophy, cataract and vitreous body malformations described in children with FAS (see section on Human studies).

Eye abnormalities

Microphthalmia is considered a sign of alcohol insult to the eye. Nakatsuji and Johnson (1984) reported the adverse effects of an intraperitoneal injection of ethanol [6.5–7 gestational day (GD)] on the primitive streak mouse embryo, subsequently altering the early morphogenesis of the optic vesicle. A small primitive optic vesicle after acute maternal ethanol administration on GD7 to mice was reported by Cook et al. (1987). Pinazo-Durán (1991) described a reduced eyeball size and lower weight in the pre- and postnatal chronically ethanol-exposed rats, a finding that was confirmed in a series of studies (Pinazo-Durán et al., 1993, 1995, 1997). These data show that both acute and chronic ethanol administration delay the eye growth.

The process of eyelid opening is considered to be an external sign of normal CNS maturation in vertebrates. The observation of a delayed eye opening in prenatally ethanol-exposed animals was firstly reported by Lancaster et al. (1982) and is a frequent finding in the literature (Gallo and Weinberg, 1982; Cohen et al., 1985; Pinazo-Durán, 1991, 1993). However, it should be considered as an additional, non-specific indicator of the effects of alcohol on the developing visual system.

Retina and optic nerve abnormalities

The retina and optic nerve have proven to be vulnerable to chemical substances during development (Silva-Araujo et al., 1991, 1993; Pearson et al., 1994). In a first approach to understand the developmental changes of the retina induced by ethanol exposure, Kennedy and Elliot (1986) assessed the differentiation of the retinal neuroblastic cell layer. Ethanol and [3H]thymidine (which is incorporated into the cell cycle and labels those cells which can thereafter be detected by autoradiography) were administered to dams on GD13. Mitotic and pyknotic cells were recorded and the width and depth of the eye and the neuroblastic layer thickness were measured 24 and 48 h after administration. The results revealed that ethanol altered the normal patterns of recruitment and loss of neural progenitors (stem cells). This strongly suggests that an acute ethanol dose, administered at a period when the neuroblasts display a high activity, may profoundly damage neuroretinogenesis and optic nerve development.

In the late 1980s and throughout the 1990s, a number of authors focused on the morphological, morphometrical and ultrastructural characteristics of the retina and optic nerve following prenatal ethanol exposure (Samorajski et al., 1986; Cook et al., 1987; Phillips et al., 1991; Pinazo-Durán, 1991; Phillips and Krueger, 1992; Pinazo-Durán et al., 1993; Ashwell and Zhang, 1994; Parson et al., 1995; Chmielewsky et al., 1997; Dangata and Kaufman, 1997; Harris et al., 2000). These studies showed that the optic nerve cross-sectional area was significantly smaller in ethanol-treated animals, than in controls. Delayed myelination and a loss of myelinated and non-myelinated optic axons were detected by light and electron transmission microscopy. Phillips et al. (1991) administered ethanol via a liquid diet to dams in the third trimester of pregnancy and to artificially reared pups fed by gastrostomy. The same findings were noted when the model of chronic ethanol administration was used. For instance, an upregulation of glial fibrillary acid protein (component of the cytoskeleton of astrocytes) and myelin basic protein (component of the myelin sheath), was detected in the pre- and postnatal ethanol-exposed rat optic nerve (Pinazo-Durán et al., 1993, 1996). Recent work (Harris et al., 2000) emphasized the adverse effects of ethanol in the number of optic axons, axonal outgrowth and myelination of the optic
nerve of rats perinatally exposed to a high dose of ethanol. The axonal loss and altered myelination may be explained partly by the underlying reduction of retinal ganglion cells, the ultrastructural changes in optic axons, and the reduced number of astrocytes and oligodendrocytes spontaneously occurring in the ethanol-exposed animals compared to the controls. A significantly reduced retinal thickness and layering and a specific loss of ganglion cells in ethanol-exposed animals, but not in controls, has been reported (Clarren et al., 1990; Ashwell and Zhang, 1994; Pinazo-Durán et al., 1995, 1997; Chmielewski et al., 1997). All these studies showed clearly that the neural tissues of the eye are important targets of alcohol toxicity. Defects in the cytoarchitecture and function of the retina and optic nerve in axonal targeting and transmission of nerve impulses through the optic path, can be considered as the result of an alcohol insult to the developing visual system.

A comparison was made between the results obtained from the ophthalmological examinations of a group of Swedish children suffering from FAS (Strömland, 1985, 1987) and data from an experimental rat model of FAS (Pinazo-Durán, 1991; Pinazo-Durán et al., 1993; Strömland and Pinazo-Durán, 1994). The most frequent findings in humans were optic nerve hypoplasia and increased tortuosity of the retinal vessels (Fig. 1A and B). The offspring of the chronically ethanol-fed rats had a significantly reduced eyeball weight, loss of retinal ganglion cells and optic axons, delayed gliogenesis and myelination and a smaller optic nerve cross-sectional area and retinal thickness (Fig. 1C and D). In another study by Pinazo-Durán et al. (1997), the abnormalities of the animals did not change throughout the postnatal development or in adulthood, and Strömland and Hellström (1996) also reported that the human eye pathology remained stable throughout childhood. It seems as if prenatal alcohol exposure irreversibly damages the retina and optic nerve of both humans and rats.

**Mechanisms of prenatal alcohol toxicity**

During the last few years, new assays in neuroscience and the advance of microtechnology have encouraged the study of the molecular aspects of alcohol toxicity. Genes involving neurochemical mechanisms and alcohol metabolism have been suggested as responsible for the individual’s susceptibility to alcoholism (Mullan, 1989; Foroud et al., 1998), and genetic risk factors underlie the pathological manifestations of ethanol/acetaldehyde in the developing tissues (Ding et al., 1998). HOX and PAX genes are characterized by encoding potential signalling molecules and transcription factors that regulate region-specific cell growth and differentiation and particularly organize the cephalic region. HOX 1.5 gene has been linked to
the craniofacial malformations of FAS (Johnston and Bronsky, 1991, 1995). A number of investigations, such as those by Levine and Schechter (1993), have succeeded in identifying specific HOX and PAX genes in the developing and adult retina. The potential role of these types of genes in ethanol-related eye anomalies needs further investigation.

It has been described that both acute and chronic alcohol intoxication induce oxidative stress, with the formation of damaging free radicals and derangement of antioxidant defence in the cells of the rat, both of the developing and the adult eye (Pinazo-Durán et al., 1998, 1999a). Alcohol may produce its effects by interacting with cell membranes and receptors and by modifying the morphology and function of proteins that regulate signal transduction, gene expression, cell differentiation and proliferation (Armant and Saunders, 1996; Ding et al., 1998). The ethanol-induced changes in the physical properties of biological membranes and the lack of appropriate adaptation mechanisms may contribute to altering the cell response to positive or negative signalling, resulting in morphological and physiological abnormalities in the eyes. Using a recent technique (Iborra et al., 1998, 2001) of incorporating bromouridine into the retina and optic nerve of ethanol-exposed rats, and performing immunocytochemical assays by electron transmission microscopy, it was demonstrated that RNA synthesis and the density of the transcripts were significantly reduced in the ethanol-exposed eye tissues (Pinazo-Durán et al., 1999b). Freund et al. (1996) emphasized the fact that genes encoding 14 transcription factors are essential for normal eye development. These authors raised the question that high levels of ethanol/acetaldehyde during gestation may disturb the intrinsic mechanisms of gene expression and compromise the dynamics of ocular tissue development.

Acute and chronic ethanol administration during development suppresses cell proliferation in the brain cortex (Guerrero et al., 1990) and the normal patterns of recruitment and loss of neural progenitor cells, damaging neuroretinogenesis and optic nerve development (Kennedy and Elliot, 1986). Cartwright and Smith (1995) proposed that a single dose of ethanol (35–42 mg/dl), injected in ovo at gastrulation, enhanced cell death within areas responding to cranial neural crest cell activity, including the eyes. Sulik et al. (1988) and Ikonomidou et al. (2000) also suggested the apoptotic basis of FAS. The ventricular zone, site of mitosis of the neuroepithelial cells (considered the origin of multipotent cells), the intermediate area corresponding to the grey matter and the margins (precursors of the white matter), are located in the side walls of the neural tube. Recent research has demonstrated that neurogenesis is not only restricted to the gestational period of CNS histogenesis, as previously assumed. It seems that, under special conditions, cortical neurogenesis can occur also in the adult brain (Doetsch et al., 1999; Johansson et al., 1999). New concepts of postnatal neurogenesis in the adult vertebrate brain within specific areas containing self-renewing stem cells (with the crucial role of generating neurons and glial cells) are emerging and demand our attention. There is also a growing interest in the possible impact of stem cells on therapeutic approaches regarding neural transplantation and regeneration. The importance of this research area for ophthalmological use, including the ethanol-induced irreversible eye conditions, remains to be investigated.

GENERAL CONCLUSIONS AND COMMENTS

When reviewing the current ophthalmological literature on FAS, we noted that most work has been done in animals, while human clinical and epidemiological studies are scarce. This is surprising, as the eyes provide such a good opportunity for research in this field. The eyes of children with FAS are frequently adversely affected. Vision is often impaired and there is a wide spectrum of abnormalities, from which optic nerve hypoplasia stands out as the most typical. Present research confirms that the ocular dysmorphology and dysfunction in FAS are irreversible, as are other CNS disturbances. An eye examination offers a valuable tool in making the diagnosis of alcohol-related birth defects. The ocular manifestations, added to the somatic abnormalities and psychomotor deficiencies, aggravate the life-long handicap of the children.

Comparison of the results from the animal experiments of chronic alcoholism and the clinical experience of children with FAS, for example regarding optic nerve hypoplasia, strongly suggests that similar pathogenic mechanisms are responsible for the alcohol damage in utero to the eyes and vision. In spite of current research, the mechanisms of ethanol damage to the eyes and vision are poorly understood. Several problems may interfere with the experimental animal models dealing with the ophthalmological aspects of FAS, such as genetic differences in ethanol metabolism of the animals used, difficulties in establishing a valid dose–response level for ethanol effects and the co-existence of unknown environmental factors specific to the animal used. The eye consists of many different structures with various physiological properties, which may be difficult to isolate, process or analyse. By the use of appropriate animal models, our understanding of the cellular and molecular mechanisms of the action of alcohol in the developing eyes might improve.

FAS is a major public health problem occurring all over the world. To manage the adverse effects of alcohol exposure in utero, a team approach is needed, consisting of experts from different fields — medical, educational, social authorities and others. The alcohol-related birth defects also have great economic consequences to society. The ultimate goal is to eradicate FAS — a totally preventable condition.

REFERENCES


