

Ocular teratogens: old acquaintances and new dangers

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Abstract

Recent research into animal studies has contributed significantly to understanding the pathophysiology of some well-known teratogens, such as alcohol. Techniques, such as positron emission tomography (PET) and retinal synaptogenesis studies, have helped determine the specific areas in the developing brain and ocular structures, which are targeted by various teratogens. In this article, we also highlight a few newer agents, such as benzodiazepines, with potential for ocular malformation and morbidity in the developing foetus.

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Introduction

Teratology is the study of the causes and biological processes leading to abnormal development and birth defects and of the appropriate measures for prevention. Although genetics and other branches of medical science have justifiably received great attention in recent years for their huge contribution to our understanding of disease and malformations, teratology has been somewhat neglected. We feel, however, that teratology deserves greater attention for its continuing contribution to congenital malformations. This review article aims to familiarise the clinician with the ocular manifestations of teratogenic agents, enabling diagnosis and avoiding unnecessary investigations. The principal findings are summarised in Table 1.

The potential for certain environmental agents to cause foetal malformation was known to physicians, even in ancient times. The Bible, for instance warns against drinking wine or strong drink during pregnancy to have healthy children.¹ Several thousand years ago,

Charaka², the famous ayurvedic physician of ancient India wrote a treatise on organogenesis during pregnancy that recognised the teratogenic effects of alcohol.

Embryology forms the reference science for teratology. Ocular embryogenesis was first detailed by Ida Mann during 1920s–1960s.³ Malformations of the eyes are among the most common causes of childhood visual impairment in developed countries.^{4,5} Although good antenatal care is available for expectant mothers in the developed world, lack of awareness of the effect of environmental agents, such as drugs, (both therapeutic and recreational) still results in foetal malformations.

Modern teratology began with the observation in the 1920s that radiation could cause foetal malformation, such as cataract. In 1941, Gregg⁶ observed that rubella infection during early pregnancy produced ocular anomalies, such as congenital cataract.

Thalidomide, an antianxiety and antiemetic drug, that was used widely by pregnant women in the 1960s, was recognised as being responsible for severe teratogenic malformations. Lenz⁷ observed 50 children whose mothers had consumed thalidomide during pregnancy. A significant number of thalidomide children had ocular motility disorders, such as Duane's retraction syndrome.⁸ Careful investigation of children with thalidomide malformations suggested that the motility abnormalities were due to a discrete insult occurring 20–24 days after conception. Later in the 1960s, the teratogenic effects of alcohol were confirmed.⁹

Ocular embryogenesis

The cranial neural crest cells contribute mainly to the morphogenesis of the eye and face, and are particularly vulnerable to teratogenic insult.¹ The entire development process is finely controlled by an innate plan, programmed by several genes, of which *PAX 6* is the most

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Table 1 Ocular teratogens

<i>Agent</i>	<i>Principal ocular malformations</i>	<i>Principal systemic malformations</i>	<i>Possible mechanism of action</i>
<i>Substance abuse</i>			
Alcohol	ONH, coloboma, nystagmus, cataract, microphthalmos	Mild mental retardation, hyperactivity	Nerve cell apoptosis
Opioids	Nystagmus, reduced vision, delayed visual maturation	Microcephaly	Midbrain toxicity
Benzodiazepines	Nystagmus, reduced vision, delayed visual maturation		Midbrain toxicity
Cocaine	Prolonged eyelid oedema, optic nerve abnormalities, delayed visual maturation	Structural brain malformations	CNS serotonin transport
<i>Prescription medications</i>			
Thalidomide	Duanes/ocular motility disorders, lacrimation	Limb malformations	
Anticonvulsants	Myopia, prominent long eye lashes	Neural tube defects, congenital heart disease	Folate metabolism, collagen 2 production
Vitamin A	Microphthalmia, hypertelorism	Retinoic acid embryopathy, craniofacial anomalies	
<i>TORCHS infections</i>			
Toxoplasmosis	Retinochoroiditis	Microcephaly, intracranial calcification	Direct viral damage, reduced mitosis
Rubella	Cataract, glaucoma, microphthalmos, chorioretinitis	Deafness, congenital heart disease	Direct viral damage, reduced mitosis
CMV	Cataract, microphthalmos, chorioretinitis, ONH	Thrombocytopenia, splenomegaly, IUGR	Vasculitis, extensive tissue necrosis
HSV	Cataract, microphthalmos, chorioretinitis, ONH	Microcephaly, intracranial calcification	
Syphilis	Interstitial keratitis, cataract, glaucoma	Renal, hepatic manifestations, generalised lymphadenopathy	
Varicella	Blepharoconjunctivitis, keratitis, chorioretinitis, optic atrophy	Cortical visual impairment	Direct viral damage, reduced mitosis
Lymphocytic choriomeningitis virus	Chorioretinopathy, nystagmus, oesotropia, microphthalmos, cataract		
<i>Metabolic disorders</i>			
Diabetes mellitus	Optic nerve hypoplasia	Neural tube defects	Reduced PAX3 gene expression
Radiation	Cataract	Widespread anomalies	Effect on DNA

important one. In a mouse model, it has been known to play a key role in both the lens and retinal development through interaction with various transcription factors, regulating cell proliferation and differentiation. PAX 6 mutations are associated with abnormalities in all the ocular tissues, such as lens, cornea, retina, and iris. Also, ectopic expression of PAX 6 in insects and frogs has shown eye formation in these sites. Similar studies in other model organisms coupled with genetic information from human patients with ocular maldevelopments have helped establish its selective role in eye development. PAX 6 dosage of expression is critical. For instance, overexpression causes micro-ophthalmia in transgenic mice. Both environmental and genetic factors may affect this, thus affecting neuronal induction, migration, and

differentiation during early embryogenesis.¹⁰ The extent of damage to the growing embryo depends on the timing of insult, its dose, and its species specificity.^{11,12}

Foetal alcohol syndrome (FAS)

FAS is the most extreme manifestation of prenatal alcohol exposure and is characterised by the presence of signs in each of three categories;¹³ first, there is prenatal and/or postnatal growth retardation. Second is the central nervous system involvement. Third is the characteristic facial dysmorphism with at least two of the following: microcephaly, microphthalmia, short palpebral fissures, poorly developed philtrum, thin upper lip, deformed pinna, and flattening of maxillary area.

Miller *et al*¹⁴ described nine patients with typical features of FAS, five of whom had strabismus and three who had ptosis. A possible intriguing feature of FAS is that anterior segment anomalies seemed to predominate in Afro-Caribbean populations,¹⁵ whereas posterior segment abnormalities predominate in mainly Caucasian populations. Stromland and Ksiazek¹⁶ reported that most ocular anomalies occurred in the fundus, ranging from malformations of several structures to discrete lesions. The most frequent finding was unilateral or bilateral optic nerve hypoplasia (48%), followed by abnormally tortuous retinal vessels and foveal hypoplasia.¹⁶ Other features included microphthalmos, phthisis, coloboma, nystagmus, cataract, and persistent foetal vasculature.¹⁷ Ocular signs are such a frequent finding in children with FAS that an ophthalmological examination is advised in making this diagnosis. The electroretinogram may show deficits in retinal sensitivity; decreased amplitude, and increased latency, especially for rod responses.¹⁸ In a study of 11 individuals with FAS and developmental delay, optic nerve hypoplasia was present in 91%, reduced visual acuity in 91%, and abnormal MRI brain scans in all.

A conservative estimate of the incidence of FAS in the Western world is 0.33 per 1000 live births.¹⁹

The pathophysiology of FAS

Teratogenic studies in animal models have shown that ethanol affects the major neurotransmitter systems, glutamate, and γ -amino butyric acid (GABA) during a critical period of development, causing developing nerve cells to die *en masse* by apoptosis. The window of vulnerability coincides with synaptogenesis (brain growth-spurt period) that is confined to postnatal life in rodents, but which encompasses the third trimester and first several years of life in humans. Retinal synaptogenesis in humans begins around late first or early second trimester. In rodent studies, during a similar period, a single ethanol intoxication lasting several hours triggers a massive wave of apoptosis of neurons at all levels of the visual system from retina to the visual cortex within hours of ethanol administration, consistent with a primary insult to ganglion cells. Exposure of the human foetus to ethanol at any time during second or third trimester may similarly entail risk of neurons being destroyed at some level of the visual system; retina, lateral geniculate nucleus, superior colliculus, or visual cortex.²⁰ In a mammalian model of FAS in mouse embryo, embryos exposed to high ethanol were smaller and less advanced in development than were the embryos in the control group, and showed craniofacial abnormalities, such as a fusion defect of the neural tube.²¹

The optic nerve hypoplasia seen in FAS was until recently thought to result from optic nerve dysmyelination. The finding of acute apoptotic neurodegeneration, however, indicates that the changes may be secondary to the degeneration of retinal ganglion cells.²² It is difficult to determine the exact amount of maternal alcohol ingestion during pregnancy, but binge drinking can cause periodic high blood levels throughout pregnancy. Therefore, ocular structures are susceptible throughout term.

Cocaine

Cocaine can easily access the foetal circulation, and the developing visual system is vulnerable to cocaine exposure.²³ Prenatal cocaine exposure has been associated with developmental delay and structural brain abnormalities, such as septo-optic dysplasia, porencephaly, and bilateral cortical infarcts.²⁴ Newborns exposed to cocaine in utero may show marked vascular disruption in the retina manifested as superficial and deep haemorrhages. Although morphologically similar to retinal haemorrhages related to birth trauma, these haemorrhages take longer to reabsorb.²⁵

Good *et al*²⁶ reported 13 cocaine-exposed infants with optic nerve abnormalities, delayed visual maturation, and prolonged eyelid oedema. The eyelid oedema was so severe and prolonged in some cases as to be sight threatening. The authors hypothesised that the easy access of cocaine to foetal circulation, together with its neurotropic effects, help explain the optic nerve anomalies and delayed visual maturation. In infants, any of these eye abnormalities and especially the combination of them mandates a careful investigation for cocaine abuse.²⁶

Opiates

Heroin and methadone are the chief opiates associated with foetal exposure. In the United Kingdom, most pregnant heroin addicts are now on methadone programmes.

As opiate withdrawal can be more harmful to the developing foetus than continued drug exposure, no efforts are usually made to wean methadone-dependent women during pregnancy. In the neonatal period, withdrawal symptoms (neonatal abstinence syndrome) may occur and are most severe among methadone-exposed infants.²⁷ Until recently, however, little had been reported about the effects of opiates on the visual system. Gailliard and Borruat²⁸ reported transient horizontal pendular nystagmus in five neonates who received morphine for neonatal abstinence syndrome. A toxic effect of morphine on the midbrain was suggested to

explain this phenomenon. Recently, we have reported nystagmus in 14 children with a history of exposure to opiates and/or benzodiazepines during pregnancy.²⁹ All children had reduced visual acuity and most had developmental delay and delayed visual maturation. None of the children had a specific neurological diagnosis or seizure disorder, and their electrophysiological examinations, such as electroretinogram and visual-evoked potential, were normal. The nystagmus and associated clinical features were particularly associated with the combined use of opiates and benzodiazepines.

Recent research using positron emission tomography (PET) has revealed a high number of opiate receptors in the human central nervous system.³⁰ Labelled fentanyl and morphine have been used to identify these receptors, especially μ -opioid receptors.³¹ It has been shown that μ -opioid receptors are upregulated in cocaine and alcohol as nystagmus occurs in children exposed to various drugs in utero. Concurrent use of benzodiazepines may enhance the effects of opiates making nystagmus more likely in babies born to mothers who abuse both drug types as diazepam counters morphine tolerance by stopping the upregulation of central nervous system μ -opioid in animal models.³²

Foetal anticonvulsant syndrome

Distinct congenital malformations, including several ocular defects, have been well described as foetal anticonvulsant syndrome. Although there are differences in phenotypes after exposure to sodium valproate, carbamazepine, and phenytoin, significant overlap of features exists. Foetal valproate syndrome is characterised by the presence of epicanthic folds, medially deficient eyebrows, shallow nasal bridge with anteverted nares, and trigonocephaly. Wyszynski *et al*³³ reported that the greatest risk for foetal malformations, such as neural tube defects, happened with valproate exposure more than phenytoin or carbamazepine. A dose-dependent effect for valproate was also shown and supported its role as a teratogen. Observations in a small series of children with prenatal valproate exposure suggested high incidence of early onset myopia. This was confirmed in a study by Glover *et al*³⁴ of 58 children with known prenatal exposure to anticonvulsant drugs, either as valproate monotherapy or in combination with other drugs. A significantly high incidence of myopia and strabismus was seen. It was suggested that the drugs' effect on folic acid metabolism might be responsible for the neural tube defects seen in these children. *In vitro* studies have also shown valproate causing increased production of type 1 collagen, but decreased production of type 2 collagen found in vitreous. It is possible that

valproate results in myopia because of its effect on collagen 2 production.

Diabetes mellitus

Diabetic pregnancy, despite the improved metabolic control, is still a strong risk factor for alterations in foetal development, particularly in patients with a tendency to brittle glycaemia during the first trimester. Congenital malformations, including neural tube defects, are significantly increased in the offspring of diabetic mothers and have been seen in experimental organisms, such as rodents. In a mouse model of diabetic pregnancy, expression of *PAX3*, a gene encoding the transcription factor required for neural tube development, was shown to be significantly decreased, and was associated with increased frequency of neural tube defects. The proposed mechanism is increased oxidative stress in the embryo in maternal diabetes, which in turn inhibits the expression of *PAX3* gene.^{35,36}

The most common ocular malformation in babies born to diabetic mothers is optic nerve hypoplasia. Keeping fasting glucose levels in the first trimester below 5.8 mmol/l and postprandial glucose levels below 9.1 mmol/l can contribute to decreasing the number of foetal malformations in pregestational diabetes mellitus pregnancy.³⁷

Intrauterine infections

The developing embryo may be exposed to maternal infections, such as TORCH infections (ie, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex, and syphilis)³⁸⁻⁴¹ and lymphocyte choriomeningitis.⁴² These may spread either by the haematogenous route or by ascending maternal genitourinary tract or even during the delivery process. The damage to the embryo may be limited only to the developmental stage at which infection occurs or may continue into postnatal life.

Different pathogens causing intrauterine infections can produce a similar spectrum of clinical signs. They may, therefore, be indistinguishable on morphological features alone (see Table 1 for details).

Vitamin A

Hale⁴³ showed that vitamin A deficiency in female pigs produced anophthalmos and microphthalmos in its offspring. Since then, both hypo- and hypervitaminosis A have been known to be associated with foetal developmental defects. Isotretinoin or accutane is a vitamin A analogue used for treatment of severe acne. Its use during pregnancy, causing high levels of vitamin A in an expectant mother, is teratogenic and is associated

with a collection of foetal malformations known as retinoic acid embryopathy.⁴⁴ Retinoids, the synthetic derivatives of vitamin A, have a key role on cellular differentiation and developmental tissue specificity. Their effects are mediated by nuclear receptors, which transactivate homeobox genes. In animals models, they all have been shown to induce similar foetal malformations dependent on the dose and the duration of exposure, affecting the craniofacial structures, foetal neural development, and postnatal sensorineural functioning.⁴⁵ In a case report of acitrenin embryopathy, a vitamin A analogue, an infant with prenatal exposure showed microcephaly, epicanthal folds, and neurodevelopmental delay.⁴⁶

Interestingly, several characteristics of FAS are similar to the teratogenic effects of retinoic acid exposure. It has been suggested that FAS may result from ethanol-induced alteration in endogenous retinoic acid synthesis, leading to abnormal embryonic concentrations. In an animal model study of *Xenopus* embryo, it was shown that with ethanol exposure during late blastula and early gastrula stage, the formation and function of the embryonic organiser was disrupted due to a reduction in retinoic acid levels. Ethanol is antagonistic to retinol and to retinal conversion of retinoic acid. The authors suggested that this mechanism may be in part responsible for the craniofacial features seen in FAS.⁴⁷ Retinoic acid and ethanol have also been shown to reverse each others effect in studies on isolated neuroblastoma cells.⁴⁸

What else is out there?

The recreational use of drugs, such as ecstasy and cannabis, is widespread, and although we have no definite information as to their potential as teratogens, the possibility must be at least considered. These agents are used because they exert effects on the central nervous system and can all be reasonably presumed to have the potential to damage the developing nervous system. The effects of cannabinoids on the nervous system are not fully understood, and they may in fact have some neuroprotective functions.⁴⁹ The popular dance drug ecstasy is neurotoxic to central serotonergic neurons in laboratory animals, and possibly also in humans.⁵⁰

In recent years, several studies have reported alterations of serotonergic transmission and neuropsychiatric abnormalities in ecstasy users. However, the prevalence of polydrug use makes it difficult to isolate the specific effects of ecstasy alone.⁵¹ A study from Toronto on pregnant women using ecstasy found that they were generally young and single, and had a clustering of risk factors that could compromise the pregnancy and foetus.⁵²

Ophthalmologists must be aware of the potential teratogenicity of both illicit and prescribed drugs. There is a very urgent need to more widely publicise the adverse effects of these drugs, not only among those who use them but also the carers of these young adults. It is also important for the clinicians to suspect possible exposure to substance abuse in neonates in appropriate settings possibly avoiding the need for extensive and often invasive investigations to establish the diagnosis.

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