SCIENTIFIC REPORT

Nystagmus secondary to drug exposure in utero

Alan O Mulvihill, Peter D Cackett, Nick D George, Brian W Fleck

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Aim: To report the occurrence of nystagmus in children exposed to opiates and/or benzodiazepines during pregnancy, and to describe the associated ocular and systemic findings.

Methods: Clinical examination and casenote review of 14 children with nystagmus whose mothers had misused opiates and/or benzodiazepines during pregnancy.

Results: Twelve children were exposed to opiates during pregnancy, of whom nine had also been exposed to benzodiazepines. Two children were exposed to benzodiazepines alone. In the primary position, the nystagmus was a fine horizontal pendular type in 10 (71.4%) children and was a fine horizontal jerk nystagmus in the other 4 (28.6%) children. The onset of the nystagmus probably occurred in the first 6 months of life in all cases. The mean binocular best-corrected logarithm of the minimum angle of resolution visual acuity was 0.59 (20/80). Electroretinogram and visual evoked potential examinations were found to be normal in the three children tested. Nine (64.3%) children had developmental delay and at least 7 (50%) had delayed visual maturation. Six children had microcephaly and two had bilateral optic nerve hypoplasia. None of the children had a specific neurological diagnosis or seizure disorder.

Conclusion: This study strongly supports a teratogenic association between exposure to controlled drugs in utero and infantile nystagmus. Furthermore, the nystagmus and associated clinical features seem to be particularly associated with combined use of opiates and benzodiazepines. Exposure to opiates and/or benzodiazepines during pregnancy should be considered in the differential diagnosis of infantile nystagmus.

Drug misuse during pregnancy is a significant social and medical problem that is potentially harmful to the developing embryo and fetus. A relationship between brain and ocular abnormalities in infants born to mothers who misused cocaine in pregnancy has been reported previously.¹ We describe 14 children with nystagmus who were exposed to opiates and/or benzodiazepines in utero. The ocular teratogenic effects of opiates and benzodiazepines have not been reported previously.

METHODS

All children in this case series attended the paediatric eye service of two teaching hospitals (Eye Pavilion, Edinburgh, UK, and Ninewells Hospital, Dundee, UK) or their affiliated local clinics. Children with nystagmus and who had been exposed to opiates and/or benzodiazepines in utero were identified by screening the letters from the referring paediatrician or primary care physician. The history of drug exposure was recorded in as much detail as possible by casenote review and by interviewing the parents (where available), other relatives or foster parents. We can be reasonably certain that each of these children were exposed in utero to the drugs listed in table 1. It is certainly

possible, however, that some or all of the children may have been exposed to other controlled drugs or alcohol.

Information on associated systemic or neurological problems was obtained from the casenotes.

All the identified children were examined by an experienced paediatric ophthalmologist. All the children had a thorough eye examination including an age-appropriate assessment of visual acuity with Cardiff acuity cards, Snellen single letters or Snellen linear charts. Visual acuity results were recorded as logMAR equivalents. The nature of the nystagmus was recorded, along with any compensatory head posture. The ophthalmic examination included ocular motility, cover testing, cycloplegic refraction and fundus examination.

RESULTS

A total of 14 children who had been exposed to opiates and/or benzodiazepines in utero were identified. The mean age of the children at the time of examination was 37.2 months.

Drug exposure

Among the 12 children exposed to opiates, exposure continued throughout pregnancy in at least 9 (75%) cases (table 1). Of these children, the mother of one patient changed from intravenous heroin to a methadone treatment programme when she realised she was pregnant at 10 weeks gestation. Otherwise, drug use was apparently unchanged through pregnancy.

At least 11 children were exposed to benzodiazepines during gestation. All 11 children were exposed to diazepam and one child was also exposed to nitrazepam (patient 2). There was combined use of benzodiazepines and opiates in nine cases. Two children were exposed to benzodiazepines but not opiates (patients 4 and 11). Another three children were exposed to opiates but not benzodiazepines (patients 1, 10 and 13).

Ocular findings

The timing of onset of the nystagmus was difficult to determine with accuracy but in most of the cases it was noted in the first year of life and most probably before 6 months of age. The nystagmus was horizontal in all cases (table 2). Typically, the nystagmus had a fine horizontal pendular nature in the primary position, becoming jerky in lateral gaze.

The mean binocular best-corrected logMAR visual acuity was 0.59 (20/80). Electroretinogram and visual evoked potential examinations were normal in the children tested so far. Most of the children were mildly hypermetropic and one was mildly myopic. Three children had significant astigmatism (at least 1.0 D) in both eyes. Seven children had strabismus, esotropia in six cases and exotropia in one.

Two children had bilateral optic nerve hypoplasia; both children had been exposed to opiates and benzodiazepines in utero. No other retinal or macular abnormalities were found.

Abbreviation: LogMAR, logarithm of the minimum angle of resolution

Table 1 History of drug exposure

	Patient number													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age at examination (months)	18	9	12	48	37	104	48	6	12	24	118	48	19	18
Drugs:														
Heroin IV	✓						✓						✓	✓
Methadone	✓	✓	✓		✓	✓		✓	✓	✓		✓	✓	✓
Diazepam		✓	✓	✓		✓	✓	✓			✓	✓		✓
Other	Chlorpromazine				Amitriptyline		Butane	Dihydrocodeine	Cannabis	Cannabis	Dihydrocodeine	Butane		
Other								Amphetamines	Amitriptyline		Alcohol			
Exposure throughout pregnancy	✓	✓		✓	✓		✓	✓		✓			✓	✓
Neonatal abstinence syndrome	✓			✓	✓	✓			✓			✓	✓	

Systemic findings

At least seven children had signs of drug withdrawal (neonatal abstinence syndrome) after birth. At least seven children had delayed visual maturation with no demonstrable visual function until at least 3 months of age. In all, 9 (64.3%) children have had a diagnosis of developmental delay made by a paediatrician. Five children have microcephaly, although none has a specific neurologic diagnosis or seizure disorder. Three children had brain MRI as part of their neurological examination; in all three cases, the scans showed no evidence of structural brain abnormalities (table 3).

DISCUSSION

We have described 14 children with permanent horizontal nystagmus who were exposed to opiates and/or benzodiazepines in utero. This study was prompted by the observation of nystagmus in a number of children with a history of drug exposure in utero.

Data from the Information Services Division of the National Health Service Scotland have shown that the rate of neonatal discharges where the mother had a diagnosis of drug misuse has increased steadily between 1996/7 and 1999/2000, with an increase from 9.3 to 17.7 per 1000 discharges. Although this may simply represent an improved identification and recording of drug misuse, it is recognised that these figures are still an underestimate, and that they illustrate the degree of the problem faced in maternal and neonatal care (<http://www.drugmisuse.isdscotland.org/publications/01bull/full/chapter3.pdf>). The Scottish Drug Misuse Database statistics for 2004/5 reports that heroin is responsible for 68% of new

attendances and that 32% of addicts misuse benzodiazepines (<http://www.drugmisuse.isdscotland.org/publications/05dmss/05dmss.htm>). In the current study, 9 (64.3%) children had been exposed to both opiates and benzodiazepines, a higher proportion than might have been expected from the wider drug misuse statistics. This observation has led us to conclude that this is more than a chance association, and that the combination of opiates with benzodiazepines is particularly likely to result in nystagmus in infants and children.

The use of alcohol and drugs during pregnancy is harmful to the developing embryo and fetus.² The risks to the neonate include withdrawal syndromes, birth defects, intrauterine growth retardation and altered neuro-behaviour. The subsequent development, behaviour and neurological function of the infant may also be affected. The recognition of the individual contribution of a substance to adverse developmental outcome can be difficult to establish clinically, because of the use of multiple drugs inherent in drug misuse and also because of reduced maternal reporting owing to fears of stigma and potential loss of child custody.

A review of the medical literature has revealed surprisingly few reported long-term effects among infants exposed to opiates before birth. Heroin and methadone are the main opiates misused during pregnancy, and both are associated with intrauterine growth retardation.³ A neonatal withdrawal or abstinence syndrome is well described in infants born to opiate-dependent mothers.⁴ It is characterised by signs and symptoms of central nervous hyperirritability,⁵ autonomic disturbances, respiratory distress and gastrointestinal dysfunction. Transient horizontal pendular nystagmus has previously

Table 2 Ocular findings

	Patient number													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Visual acuity (logMAR)														
BCVA binocular	0.4	1	0.5	0.7	0.5	0.2	0.8	1	1	0.2	0.3	0.7	0.9	1
BCVA right						0.8	0.8					0.9		
BCVA left						0.8	1					0.7		
Optic nerve hypoplasia		✓			✓									
Delayed visual maturation		✓		✓	✓	✓		✓				✓		✓
AHP	✓		✓		✓	✓	✓			✓		✓		✓
Type of AHP	Face turn		Chin up		Face turn	Chin down	Face turn				Tilt	Face turn		Face turn
Refraction														
Right	+2.5	0	-0.5	+1.5	+1.5	+0.5/+1.0×90	+2.0	+3.0	+2.5/+1.5	0	+1.5/+2.5	+0.5	+2.0	+0.25
Left	+2.5	+0.25	-0.5	+1.5	+1.5	+0.5/+1.5×90	+1.75/+0.5	+3.0	+3/+1.5	0	+1.5/+2.5	+0.25	+2.0	0
Strabismus			ET				ET		ET	X(T)		ET	ET	ET
Electrodiagnostics														
ERG	Normal			Normal								Normal		
VEP	Not possible			Normal		Normal						Normal		

AHP, abnormal head posture; BCVA, best-corrected visual acuity; ERG, electroretinogram; ET, esotropia; logMAR, logarithm of the minimum angle of resolution; VEP, visual evoked potential; X(T), exotropia.

Table 3 Systemic findings

	Patient number													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Developmental delay	✓	✓			✓	✓	✓	✓	✓		✓	✓		
Microcephaly	✓	✓		✓	✓									
Other		FAS				ADHD					LBP			✓
MRI brain						Normal	Normal					Normal		

ADHD, attention-deficit hyperactivity disorder; FAS, fetal alcohol syndrome; LBP, learning and behavioural problems.
Microcephaly: <3rd centile (patients 2, 4, 5, 13); <10th centile (patient 1).

been reported in neonates as part of a postnatal withdrawal syndrome, and was felt to represent a form of midbrain toxicity secondary to the therapeutic use of morphine.⁶

In vivo studies of both intravenous opiate and oral diazepam have been shown to have an effect on eye movements.^{7,8} Intravenous opiates have been shown to induce transient downbeat nystagmus, whereas oral diazepam results in altered smooth pursuit eye movements. In these two cases, the eye movements observed are felt to be the result of cerebellar opiate and benzodiazepine binding sites, respectively.

Opioidergic (μ -opioid) receptors have been shown to be present in high amounts in the thalamus, prefrontal and cingulate cortex, basal ganglia and midbrain structures in humans.⁹ These μ -opioid receptors are upregulated with cocaine and opiate abuse.¹⁰ Benzodiazepine use has been shown to antagonise the upregulation of μ -opioid receptors observed in morphine-tolerant rats.¹¹ Thus, μ -opioid receptors could represent a common pathway by which both opiates and benzodiazepines may cause nystagmus either alone or in combination.

In this study, a significant number of children were detected with nystagmus, reduced vision and developmental delay following exposure to opiates and/or benzodiazepines in utero. We hypothesise that the nystagmus secondary to drug exposure in utero is a direct teratogenic effect possibly occurring as a result of abnormal μ -opioid receptor binding in the cerebellum of the developing embryo and fetus. The combined use of benzodiazepines with opiates may have a synergistic effect. These findings are significant in several respects. Firstly, ophthalmologists must consider prenatal drug exposure in the differential diagnosis of infantile or childhood nystagmus, and reduced vision. Secondly, the view that opiates and/or benzodiazepines are not significantly teratogenic must be revised. Finally, it must be recognised that medications prescribed as part of drug treatment programmes may be teratogenic, and female drug users must be advised of the potential risks to the fetus.

Drug exposure during pregnancy should be considered in the differential diagnosis of infants presenting with nystagmus, reduced vision and developmental delay. Opiates and/or benzodiazepines may have a direct teratogenic effect alone or in combination on the developing fetus, resulting in permanent nystagmus and reduced visual acuity. We acknowledge that while our study is suggestive of an association between maternal opiate and benzodiazepine misuse and nystagmus,

further research in the form of a case-control study may provide stronger evidence for this.

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Authors' affiliations

A O Mulvihill, P D Cackett, B W Fleck, Princess Alexandra Eye Pavilion, Edinburgh, UK

N D George, Ninewells Hospital, Dundee, UK

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Correspondence to: Dr P D Cackett, Princess Alexandra Eye Pavilion, Chalmers Street, Edinburgh EH3 9HA, UK; pete@pdcackett.demon.co.uk

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