УДК 617.761–009.24

Mulvihill A. O.[1], Cackett P. D.[1], George N. D.[2], Fleck B. W.[1]
[1]Princess Alexandra Eye Pavilion, Edinburgh, United Kingdom
[2]Ninewells Hospital, Dundee, United Kingdom

Nystagmus secondary to drug exposure in utero

SUMMARY

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 fourteen 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 ten (71.4 %) children and was a fine horizontal jerk nystagmus in the other four (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 seven (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.

Keywords: nystagmus, children, exposition, opiates, benzodiazepines, pregnancy.

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 fourteen 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.

Table 1
History of drug exposure

Parameters	Patient number						
	1	**2**	**3**	**4**	**5**	**6**	**7**
Age at examination (months)	18	9	12	48	37	104	48
Drugs							
Heroin IV	٧	–	–	–	–	–	٧
Methadone	٧	٧	٧	–	٧	٧	–
Diazepam	–	٧	٧	٧	٧	٧	٧
Other	Chlorpromazine	–	–	Amitriptyline	–	–	Butane
Other	–	–	–	–	–	–	–
Exposure throughout pregnancy	٧	٧	–	٧	٧	–	٧
Neonatal abstinence syndrome	٧	–	–	٧	٧	٧	–
Parameters	**Patient number**						
	8	**9**	**10**	**11**	**12**	**13**	**14**
Age at examination (months)	6	12	24	118	48	19	18
Drugs							
Heroin IV	–	–	–	–	–	٧	٧
Methadone	٧	٧	٧	–	٧	٧	٧
Diazepam	٧	٧	–	٧	٧	–	٧
Other	Dihydrocodeine	Cannabis	Cannabis	Dihydrocodeine	Butane	–	–
Other	Amphetamines	Amitriptyline	–	Alcohol	–	–	–
Exposure throughout pregnancy	٧	٧	٧	–	–	٧	–
Neonatal abstinence syndrome	–	٧	–	–	٧	٧	–

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 logarithm of the minimum angle of resolution (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

Fourteen 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 twelve children exposed to opiates, exposure continued throughout pregnancy in at least 9 (75 %) cases (see 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 eleven children were exposed to benzodiazepines during gestation. All eleven children were exposed to diazepam. One child was also exposed to nitrazepam (patient 2). There was combined use of benzodiazepines and opiates in 9 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). Electro-retinogram 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.

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, nine (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 magnetic resonance imaging (MRI) as part of their neurological examination; in all 3 cases the scans showed no evidence of structural brain abnormalities (table 3).

Table 2
Ocular findings

Parameters	Patient number						
	1	**2**	**3**	**4**	**5**	**6**	**7**
Visual acuity (logMAR)							
BCVA binocular	0.4	1	0.5	0.7	0.5	0.2	0.8
BCVA right	–	–	–	–	–	0.8	0.8
BCVA left	–	–	–	–	–	0.8	1
Optic nerve hypoplasia	–	٧	–	–	٧	–	–
Delayed visual maturation	–	٧	–	٧	٧	٧	–
AHP	٧	–	٧	–	٧	٧	٧
Type of AHP	Face turn	–	Chin up	–	Face turn	Chin down	Face turn
Refraction							
Right	+2.5	0	–0.5	+1.5	+1.5	+0.5/+1.0 × 90	+2.0
Left	+2.5	+0.25	–0.5	+1.5	+1.5	+0.5/+1.5 × 90	+1.75/+0.5
Strabismus	–	–	ET	–	–	–	ET
Electrodiagnostics	–	–	–	–	–	–	–
ERG	Normal	–	–	Normal	–	–	–
VEP	Not possible	–	–	Normal	–	Normal	–
Parameters	**Patient number**						
	8	**9**	**10**	**11**	**12**	**13**	**14**
Visual acuity (logMAR)							
BCVA binocular	1	1	0.2	0.3	0.7	0.9	1
BCVA right	–	–	–	–	0.9	–	–
BCVA left	–	–	–	–	0.7	–	–
Optic nerve hypoplasia	–	–	–	–	–	–	–
Delayed visual maturation	٧	–	–	–	٧	–	٧
AHP	–	–	–	٧	٧	–	٧
Type of AHP	–	–	–	Tilt	Face turn	–	Face turn
Refraction							
Right	+3.0	+2.5/+1.5	0	+1.5/+2.5	+0.5	+2.0	+0.25
Left	+3.0	+3/+1.5	0	+1.5/+2.5	+0.25	+2.0	0
Strabismus	–	ET	X(T)	–	ET	ET	ET
Electrodiagnostics	–	–	–	–	–	–	–
ERG	–	–	–	–	Normal	–	–
VEP	–	–	–	–	Normal	–	–

Note. AHP – abnormal head posture; BCVA – best-corrected visual acuity; ERG – electroretinogram; ET – esotropia; VEP – visual evoked potential; X(T) – exotropia.

Table 3
Systemic findings

Parameters	Patient number													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Developmental delay	٧	٧	–	–	٧	٧	٧	٧	٧	–	٧	٧	–	–
Microcephaly	٧	٧	–	٧	٧	–	–	–	–	–	–	–	٧	–
Other	–	FAS	–	–	–	ADHD	–	–	–	–	LBP	–	–	–
MRI brain	–	–	–	–	–	Normal	Normal	–	–	–	–	Normal	–	–

Note. 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).

DISCUSSION

We have described fourteen 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 1996/1997 and 1999/2000, with an increase from 9.3 to 17.7 per 1,000 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. The Scottish Drug Misuse Database statistics for 2004/2005 reports that heroin is responsible for 68 % of new attendances and that 32 % of addicts misuse benzodiazepines. In the current study, nine (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 neurobehaviour. 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 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 occuring 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.

ACKNOWLEGEMENTS

We thank Dr. Chris Scott (Aberdeen Royal Infirmary) and Dr. Shona Sutherland (Queen Margaret's Hospital, Dunfermline), who each contributed a case to this study.

FOOTNOTES

Competing interests: none declared.

Мулвіхілл А. О.[1], Каккет П. Д.[1], Джордж Н. Д.[2], Флек Б. В.[1]
[1]Очний госпіталь принцеси Олександри, м. Единбург, Великобританія
[2]Лікарня Нінвельс, м. Данді, Великобританія

Вторинний ністагм після внутрішньоутробної дії препаратів

Резюме. Розглянуто випадки появи ністагму в дітей за внутрішньоутробного впливу опіатів і/або бензодіазепінів під час вагітності та описано відповідні очні та системні прояви. Обстежено та проаналізовано історії хвороб 14 дітей із ністагмом, чиї матері зловживали опіатами та/або бензодіазепінами під час вагітності. Внутрішньоутробний вплив дії опіатів мали 12 дітей: чіткий горизонтальний маятникоподібний ністагм у 10 (71,4 %) дітей, а горизонтальний поштовхоподібний – у 4 (28,6 %) дітей. У всіх випадках ністагм найімовірніше розвинувся в перші 6 місяців життя. Дані електроретинограми практично в усіх випадках були в межах норми. У 9 (64,3 %) дітей зазначено затримку розумового розвитку, у 7 (50 %) – затримку фізичного розвитку, у 6 – мікроцефалію, у 2 – двосторонню гіпоплазію зорового нерва, коли немає чіткого діагнозу психічного розладу. Дані підтверджують тератогенність наркотичних препаратів цієї групи та зв'язок між впливом контрольованих наркотиків і вродженим ністагмом. Вплив опіатів і/або бензодіазепінів на вагітних слід ураховувати за прогнозування та подальшої диференціальної діагностики дитячого ністагму.

Ключові слова: ністагм, діти, експозиція, опіати, бензодіазепіни, вагітність.

Мулвихилл А. О.[1], Каккет П. Д.[1], Джордж Н. Д.[2], Флек Б. В.[1]
[1]Глазной госпиталь принцессы Александры, г. Эдинбург, Великобритания
[2]Больница Нинвельс, г. Данди, Великобритания

Вторичный нистагм в ответ на внутриутробное воздействие препаратов

Резюме. Рассмотрены случаи появления нистагма у детей с внутриутробным влиянием опиатов и/или бензодиазепинов во время беременности, описаны соответствующие глазные и системные проявления. Обследованы и проанализированы истории болезни 14 детей с нистагмом, чьи матери злоупотребляли опиатами и/или бензодиазепинами во время беременности. Внутриутробное воздействие опиатов имели 12 детей: четкий горизонтальный маятникообразный нистагм у 10 (71,4 %) детей, а горизонтальный толчкообразный – у 4 (28,6 %) детей. Во всех случаях нистагм появился, вероятнее всего, в первые 6 месяцев жизни. Электроретинограммы и зрительные вызванные потенциалы были в пределах нормы у 3 обследованных детей. У 9 (64,3 %) детей отмечена задержка умственного развития и у 7 (50 %) – задержка физического развития. У 6 детей диагностирована микроцефалия, а у 2 – двусторонняя гипоплазия зрительного нерва. Данные подтверждают тератогенность наркоти-

ческих препаратов этой группы и связь между воздействием контролируемых наркотиков и врожденным нистагмом. Влияние опиатов и/или бензодиазепинов на беременных следует учитывать в прогнозировании и в дальнейшей дифференциальной диагностике детского нистагма.

Ключевые слова: нистагм, дети, экспозиция, опиаты, бензодиазепины, беременность.

REFERENCES

1. Dominguez R., Aguirre Vila-Coro A., Slopis J. M., Bohan T. P. Brain and ocular abnormalities in infants with in utero exposure to cocaine and other street drugs. *American Journal of Diseases of Children.* 1991; (145): 688–695.
2. Chiriboga C. A. Fetal alcohol and drug effects. *Neurologist.* 2003; (9): 267–279.
3. Vance J. C., Chant D. C., Tudehope D. I., Gray P. H., Hayes A. J. Infants born to narcotic dependent mothers: physical growth patterns in the first 12 months of life. *Journal of Paediatrics and Child Health.* 1997; (33): 504–508.
4. Osborn D. A., Cole M. J., Jeffery H. E. Opiate treatment for opiate withdrawal in newborn infants. *Cochrane Database of Systematic Reviews.* 2005. doi: 10.1002/14651858.CD002059.pub3.
5. Nelson N. M. *Current therapy in neonatal and perinatal medicine.* St Louis, CV Mosby, 1984.
6. Gaillard M. C., Borruat F. X. New finding: transitory horizontal pendular nystagmus secondary to neonatal abstinence syndrome. *Klinische Monatsblätter für Augenheilkunde.* 2002; (219): 317–319.
7. Rottach K. G., Wohlgemuth W. A., Dzaja A. E., Eggert T., Straube A. Effects of intravenous opioids on eye movements in humans: possible mechanisms. *Journal of Neurology.* 2002; (249): 1200–1205.
8. Rothenberg S. J., Selkoe D. Specific oculomotor deficit after diazepam. II. Smooth pursuit eye movements. *Psychopharmacology (Berl).* 1981; (74): 237–240.
9. Sprenger T., Berthele A., Platzer S., Boecker H., Tölle T. R. What to learn from in vivo opioidergic brain imaging? *European Journal of Pain.* 2005; (9): 117–121.
10. Gorelick D. A., Kim Y. K., Bencherif B., Boyd S. J., Nelson R., Copersino M., Endres C. J., Dannals R. F., Frost J. J. Imaging brain mu-opioid receptors in abstinent cocaine users: time course and relation to cocaine craving. *Biological Psychiatry.* 2005; (57): 1573–1582.
11. Tejwani G. A., Sheu M. J., Sribanditmongkol P., Satyapriya A. Inhibition of morphine tolerance and dependence by diazepam and its relation to mu-opioid receptors in the rat brain and spinal cord. *Brain Research.* 1998; (797): 305–312.

Стаття надійшла в редакцію 12.08.2015 р.
Рецензія на статтю надійшла в редакцію 20.09.2015 р.