Neonatal Abstinence Syndrome Not only Neonatal and Not only Abstinence



Women's & Children's Health Medicine





Neonatal Abstinence Syndrome (NAS): Newborn Withdrawal from Maternal Drugs



Chronic exposure

No more drugs

Withdrawal

NAS is a Global Public Health Epidemic







One baby born every 15 minutes



300% increase over 10 years



Hospital costs >6X since early 2000's Mostly public funds

NAS can Kill

1875 WITHDRAWAL STARTS IN A FEW DAYS IN OTHERWISE NORMAL BABIES



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A rare and little known cause of convulsions in the newborn is congenital morphinism. Although unmentioned in standard textbooks of pediatrics or medicine, it is known to physicians whose patients include morphine addicts and who thus have learned that children born to addicted mothers often die in the first week of life. The infants are born at full term and are apparently normal, but their addiction matches that of their mothers. Separation from the maternal circulation shuts off the supply of drug to the newborn, and withdrawal symptoms ensue within three days.

Infrequent reports of congenital morphinism have appeared in the literature, the first in 1875.¹ In 1892 Happel reported the cases of 12 infants born to mothers who were drug addicts. Nine of the 12 infants died.² In 1900 he added 5 more cases.³ In 1903 a correspondent, O. D., wrote in "Queries and Minor Notes" of THS JOURNAL⁴ of a baby born to a mother who had been addicted to morphine for three years. At birth the infant appeared normal, but on its second day it began to cry and continued to do so for two days, until treated with morphine $\frac{1}{120}$ grain (0.5 mg.) every other day. In 1912 Pettey reported on 20 infants born to 4 addicted mothers. One of these mothers had 16 infants, all but the last of whom died. The last infant was treated early and made an uneventful recovery.³ In 1920 Burnett reported a case in which symptoms



One mother had 16 babies 15 died

Without Treatment

9/10 babies with NAS will die



Goodriend et al 1956 **Overall mortality 34%**



Ref: Goodfriend 1956, Perlstein 1945

Now with prompt recognition and treatment, NAS is an uncommon direct cause of infant death Most babies with NAS will survive

What happens to them?

Children with NAS are hard to find

- ~>1000 known NAS infants in NSW alone each year
- Mobile
- Difficult to engage
- Social and Environmental Problems
- •Healthy



Data Linkage can be used to find children with NAS in NSW



We tracked >3800 children with NAS to 12 years



Mums

| | NAS (n = 3,803) | No NAS (n = 1,003,012) | OR (95% CI) | |
|-----------------------------|--------------------|---------------------------|-----------------------|----|
| Mean maternal age, yrs | 29.1 (5.8)* | 30.4 (5.6) | | |
| Indigenous ethnicity | 15.6% | 2.8% | 6.4 (6.0-7.0)* | |
| Cigarette smoking | 76.9% | 12.4% | 23.6 (21.8- 25.4)* | |
| No antenatal care | 8.4% | 1.4% | 6.6 (5.9-7.4)* | |
| Lowest Economic Quintile | 13.3% | 8.9% | 1.6 (1.4-1.7)* | *۲ |

Babies

| | NAS | No-NAS | OR (95% CI) | |
|------------------------|--------------|---------------|-----------------|-----|
| | (n=3,842) | (n=1,018,421) | | |
| Male | 52.5% | 51.4% | 1.0 (0.9-1.1) | |
| Low Birthweight <2500g | 25.0% | 5.8% | 5.4 (5.1-5.9)* | |
| <37wks gestation | 22.4% | 6.7% | 4.0 (3.7-4.3)* | |
| Apgar <7 at 5 minutes | 3.7% | 1.4% | Each day in | the |
| Admission to nursery | 74.6% | | , nurserv co | sts |
| Length of stay, days | 10.0* | 3.0 | ~\$6000 | |
| (median) | | | , | |

Children with NAS were Hospitalized More Often After Birth

| | NAS | Non-NAS | OR (95% CI) |
|----------------------|-----------|---------------|----------------|
| | (n=3,837) | (n=1,016,565) | |
| Episodes of Care | 5,154 | 887,227 | |
| Admitted after birth | 52% | 40% | 1.6 (1.5-1.7)* |
| Number of episodes | 1.3/child | 0.9/child | |
| Mean total episodes | 2.1±4.0* | 1.6±3.8 | |

*p<0.001

Even until adolescence



They were Hospitalized for External Reasons (not illnesses)

| ICD10 Classification | Number of children (%) | | | |
|---|--------------------------------|--------------|-------------------|--|
| | NAS (n=3,837) (n=1,016,565) | | OR (95% CI) | |
| Injury, poisoning & consequences of external causes | 478 (12.5) | 69,977 (6.9) | 1.9 (1.8-2.1)* | |
| Burns and corrosions | 41 (1.1) | 4,139 (0.4) | 2.6 (1.9-3.6)* | |
| Poisoning | 43 (1.1) | 3,231 (0.3) | 3.6 (2.6-4.8)* | |
| Maltreatment (neglect & abuse) | 28 (0.7) | 355 (0.0) | 21.0 (14.3-31.0)* | |
| Accidents | 440 (11.5) | 64,497 (6.3) | 1.9 (1.7-2.1)* | |
| Assault | 45 (1.2) | 791 (0.1) | 15.2 (11.3-20.6)* | |
| *p<0.001; **p<0.05 | | | | |

Median age (months): 4^{**} vs 11

They were also hospitalized for Mental and Behavioural Disorders

| ICD10 Classification | Number of children (%) | | | |
|------------------------------------|-------------------------|-------------------------|----------------|--|
| | NAS (n=3,837) | No NAS (n=1,016,565) | OR (95% CI) | |
| Mental & behavioural disorders | 96 (2.5) | 9924 (1.0) | 2.6 (2.1-3.2)* | |
| Mental Retardation | 13 (<mark>0.3</mark>) | 1,238 (0.1) | 2.8 (1.6-4.8)* | |
| Psychological development disorder | 39 (1.1) | 3,592 (0.4) | 2.9 (2.1-4.0)* | |
| Speech/language disorder | 12 (0.3) | 887 (0.1) | 3.6 (2.0-6.4)* | |
| Autism | 15 (0.4) | 1,113 (0.1) | 3.6 (2.2-6.0)* | |
| Behavioural & emotional disorders | 32 (0.8) | 2,090 (0.2) | 4.1 (2.9-5.8)* | |
| *p<0.001 Median age (year | s): 5.4 * | vs 3.4 | | |

Are Children with NAS More Likely to Die?





Yes – at 3x the rate of other children

| # of deaths (% of deaths) | | | | |
|----------------------------|-----------------|--------------|-----------------|--|
| | NAS | No NAS | OR(95% CI) | |
| Death before discharge | 5 (11.1) | 1856 (50.6) | 0.7 (0.3-1.7) | |
| 0 – <28 days | 8 (17.8) | 1,809 (49.5) | 1.2 (0.6-2.4) | |
| 28 days – 1 yr | 30 (66.7) | 1,051 (28.6) | 7.6 (5.3-11.1)* | |
| 1-4 yrs | 5 (8.9) | 547 (12.2) | 2.4 (1.0-5.9) | |
| >4 yrs | 2 (6.7) | 258 (9.7) | 2.1 (0.5-8.3) | |
| Total | <u>45 (100)</u> | 3,665 (100) | 3.3 (2.4-4.4)* | |
| Death rate | 1.2% | 0.4% | | |
| *p<0.001 | | | | |

And even until adolescence



Why they die was usually unclear

| | Admission before Death | | |
|-----------------------|------------------------|---------------------------|--|
| | NAS | No NAS | |
| Mean total admissions | 1.8±1.8* | 3.3±8.3 | |
| Postmortem | | | |
| | NAS | No NAS OR(95% CI) | |
| Autopsy performed | 16 (59.3) | 905 (29.2) 3.5 (1.6-7.6)* | |
| | | | |

*p<0.001

And not related to illness

| | NAS (n=3,842) | No NAS (n=1,018,421) | OR (95% CI) | Ρ |
|---|------------------|-------------------------|---------------------|-------|
| ICD-10 Code | # of death | s (% of deaths) | | |
| Perinatal conditions | 6 (20.0) | 811 (36.5) | 2.0 (0.9 – 4.4) | 0.14 |
| Congenital & chromosomal abnormalities | 0 | 522 (23.5) | _ | - |
| III-defined causes | 15 (50.0) | 272 (12.2) | 14.7 (8.7 – 24.7) | <0.00 |
| Sudden Infant Death Syndrome | 8 (26.7) | 198 (8.9) | 10.7 (5.3 – 21.8) | <0.00 |
| External causes | 8 (26.7) | 166 (7.5) | 12.8 (6.3 – 26.0) | <0.00 |
| Accidents | 4 (13.3) | 144 (6.5) | 7.4 (2.7 – 19.9) | 0.002 |
| Assault | 3 (10.0) | 20 (0.9) | 39.8 (11.8 – 134.0) | <0.00 |

What about school?

- School failure:
- Physical problems
- Psychological problems
 - Depression
 - Anxiety
- Lower earning potential
- Adjustment in society









How do children with NAS do at school?

Don't know: but Children with NAS Have Multiple Risks for Poor Learning

- Direct drug effects?
- Parenting
 - Parental psychiatric co-morbidities
 - Low parental education
 - Genetics

• Social

- School and home mobility
- Poverty
- Poor nutrition



Is there a biological basis for poor learning? Almost all drugs cross the placenta

But not all drugs cause structural abnormalities of the brain



Normal 6 week brain

Brain of baby of alcoholic mother

Brain is Formed by 1st Trimester



Most drugusing mothers will engage in antenatal care only in the 2nd trimester

But some drugs can affect Brain GROWTH AND DEVELOPMENT

- 1. Opioids disrupt:
 - 1. Myelin production
 - 2. Dendritic length
 - 3. Axonal Branching
- 2. Neuronal death by **apoptosis and necrosis**
- 3. Increases vascular contractility: potential **hypoxemia** to brain and placenta
- 4. Stimulate Opiate Receptors (negative growth factor)





Short, simple dendrites Small brain

What happens to the brains of babies with NAS?





Brain MRI Of 32 Babies Exposed To Prenatal Opioids

Babies of mothers who used only one opioid e.g. methadone/buprenorphine

Vs

Babies of mothers who used multiple opioids e.g. methadone + heroin

Hypothesis: Babies of opioid-using mothers have small but structurally normal brains

No money for MRIs of drug free babies \mathfrak{B}

Babies of Mothers Who Used > 1 Opioid had smaller brains





And Very Small Cerebellums





How do Children with NAS do at School?

THE NAPLAN TEST – National Assessment Program-Literacy and Numeracy

- Australia-wide COMPULSORY Test
- Introduced in 2008
- Test is taken in May each year
- Results available in September
- Each student assessed 4 times in school life:
 - Year 3 ages 8-9
 - Year 5 ages 10-11
 - Year 7- ages 12-13
 - Year 9- ages 14-15

| NAPLAN YEAR 3 |
|----------------------|
| LANGUAGE CONVENTIONS |
| WRITING |
| READING |
| N U M E R A C Y |

NAPLAN Tests

- Aimed to identify children not meeting national minimum standards (~10-20%)
- Exemptions uncommon (very sick, newly arrived from non-English speaking country)
- NSW sitting rate >95%

Children BELOW Minimum Standards do not have skills to proceed on to the next level of school





Children with NAS were 20% more likely than rest of population or controls to not have a NAPLAN record

Almost ¹/₂ of NAS children failed to meet minimum standards by year 5



In high school, test scores of NAS children were lower than other children who were 2 years younger



How do children with NAS compare to other sick children?



Floyd 24 weeks 500g Born 1998 Chances of survival: <50%



Robert Term NAS Born in 1998 Chances of survival >95%

What Happened to Floyd and Robert?

Floyd at 16





Robert ?

How would Floyd or Robert do in the Naplan test?



YLevel



We need to think beyond NAS

- Problems caused by NAS does not stop in the neonatal period or withdrawal
- The impact of prenatal exposure may be subtly enduring and profoundly damaging to the child
- □ Further research needs to be done for prevention and amelioration of maternal substance abuse.

Thank you