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Dr. Karishma Rao is a clinical assistant professor within the Division of Neonatology at Children's Mercy, Kansas City. Her interests include NEC and BPD. It was during her Neonatology fellowship at Children's Mercy itself that she first developed an interest in neonatal pain and infant delirium. The concept of delirium in neonates is poorly understood at this time but she hopes to shed light on it as it gains some mainstream interest.

INFANT DELIRIUM

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OVERVIEW

- DEFINITION
- MECHANISM/PATHOPHYSIOLOGY
- PHARMACOKINETICS (PK)
- RISK FACTORS
- SIGNS AND SYMPTOMS
- ADVERSE OUTCOMES
- LITERATURE REVIEW
- MANAGEMENT
- TAKE HOME POINTS

DELIRIUM OR ACUTE BRAIN DYSFUNCTION

- Delirium is defined as an acute and fluctuating change in awareness and cognition
- In the setting of a medical illness
- Incidence of approximately 17% in the PICU setting
- Uncommonly recognized in the NICU
- It is a well known and prevalent problem in the adult intensive care units

POSSIBLE CAUSES OF PEDIATRIC DELIRIUM

Infections	Encephalitis, meningitis, urinary tract infection, pneumonia…
Withdrawal	Alcohol, barbiturates, benzodiazepines…
Acute metabolic	Electrolyte imbalance, hepatic or renal failure…
Trauma	Head injury, postoperative…
CNS pathology	Stroke, haemorrhage, tumour, seizure disorder…
Hypoxia	Anaemia, cardiac failure, pulmonary embolus…
Deficiencies	Vitamin B12, folic acid, thiamine…
Endocrinopathies	Thyroid, glucose, parathyroid, adrenal…
Acute vascular	Shock, vasculitis, hypertensive encephalopathy…
Toxic or drugs	Toxins, substance intoxication, medications (alcohol, anaesthetics, anticholinergics, narcotics etc.)
Heavy metals	Arsenic, lead, mercury…

MECHANISM OF DELIRIUM

- Hypoperfusion and inflammation which occurs during critical illness plays a role
- Alterations in cerebral blood flow, disordered cellular homeostasis also play a role
- Neural ischemia leads to
  - Cortical depression due to an inability to maintain ionic gradients
  - Imbalance in neurotransmitter synthesis, release and metabolism
  - Inability to eliminate neurotoxic by-products of metabolism
- Delirium is the end result of diffuse cerebral metabolic abnormality

MECHANISM OF DELIRIUM

- Delirium is the neurobehavioral manifestation of alterations in neurotransmission
- Delirium has been associated with
  - Excess/ deficiency of dopamine
  - Acetylcholine deficiency
  - Increased GABA
- Morphine has been shown to increase the release of dopamine
- Benzodiazepines and Propofol have a high affinity for GABAergic receptors

PK OF MORPHINE IN NEONATES

- In one study, infants aged 1-4 days showed longer elimination half lives than older pts (6.8 vs 3.9 hrs)
- Clearance in newborns was less than 1/3 of that found in older infants (Aged 1d – 10w) (6.3 vs 23.8 ml/min/kg)
- Infants and neonates make relatively more M-3-G vs M-6-G
- This combination of longer half life and low clearance in infants may explain prolonged duration of action of morphine in very young infants

PK OF MIDAZOLAM IN NEONATES

- Midazolam elimination is slower in infants compared to adults
- It is mainly eliminated by hydroxylation by CYP3A4 and CYP3A5 enzymes
- These enzymes surge in the liver in the first few weeks of life
- Hence neonates have longer half lives of midazolam and slower clearance
- Multiorgan failure and severity of disease lowers the clearance of midazolam

RISK FACTORS

- Age < 2 years
- Developmentally delayed children
- Preexisting medical condition
- Severity of illness affects metabolism and PK of drugs
- Mechanically ventilated patients
- Use of benzodiazepines, narcotics, corticosteroids

SIGNS & SYMPTOMS

Irritability

Impaired alertness

Fluctuation of symptoms

Impairments of sleep-wake cycles

Inability to focus or sustain attention

SIGNS & SYMPTOMS

”Impossible to sedate”

Developmental Regression

Refractory agitation

Inability to console by usual caregivers

Reduced eye contact with the usual caregiver

ADVERSE OUTCOMES

- Increased unplanned extubations
- Longer duration of mechanical ventilation
- Prolonged hospital stays
- Developmental delays
- Strongly and independently associated with increased mortality

A case of infant delirium in the neonatal intensive care unit

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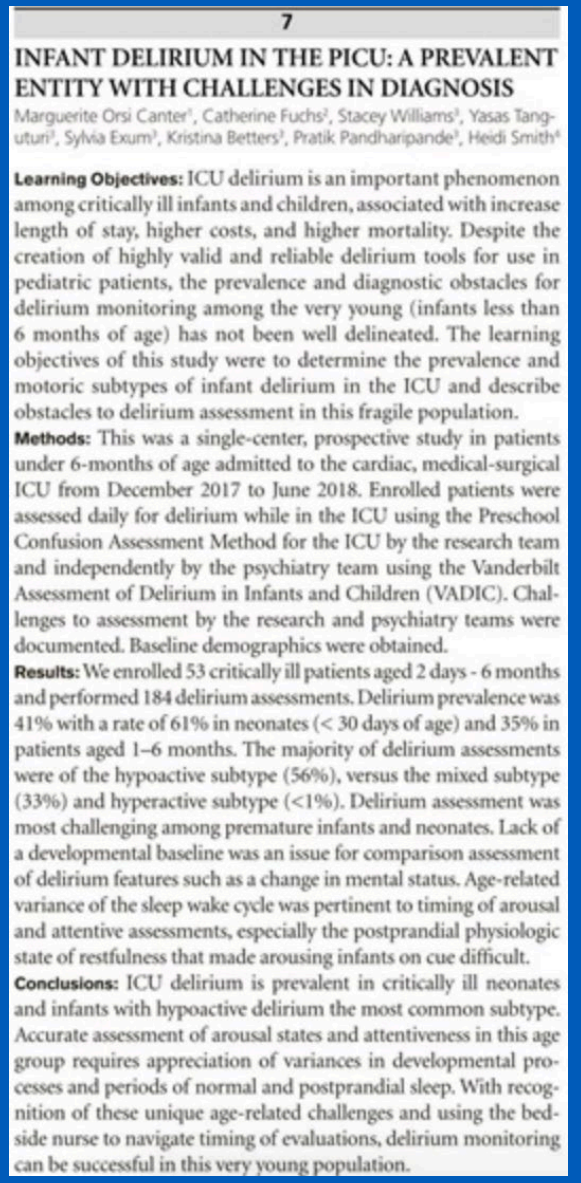
- 6 month old, born at 32 weeks, 4.7 kg male infant
- Required cardiac catheterization for evaluation of pulmonary hypertension
- Unable to extubate after the procedure
- 9 days later he was noted to have persistent agitation and was started on a versed gtt
- By day 19 he was on a fentanyl drip, midazolam drip, precedex drip
- Scheduled gabapentin, phenobarbital, methadone and diazepam

- He was noted to have purposeless movements like head shaking and arm waving
- No consistent eye contact, stopped visually tracking, did not respond to mother's voice
- Child psych was consulted on day 19 due to concern for delirium
- Infant was diagnosed with delirium
- Primary recommendation was to wean deliriogenic medications, preferably versed gtt
- Enteral risperidone was also started

Detection and Management of Delirium in the Neonatal Unit: A Case Series

Alan Groves, MBChB, MD,[a] Chani Traube, MD,[a] Gabrielle Silver, MD[b]



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INFANT DELIRIUM IN THE PICU: A PREVALENT ENTITY WITH CHALLENGES IN DIAGNOSIS

Marguerite Orsi Canter[1], Catherine Fuchs[2], Stacey Williams[3], Yasas Tanguturi[3], Sylvia Exum[3], Kristina Betters[3], Pratik Pandharipande[3], Heidi Smith[4]

Learning Objectives: ICU delirium is an important phenomenon among critically ill infants and children, associated with increase length of stay, higher costs, and higher mortality. Despite the creation of highly valid and reliable delirium tools for use in pediatric patients, the prevalence and diagnostic obstacles for delirium monitoring among the very young (infants less than 6 months of age) has not been well delineated. The learning objectives of this study were to determine the prevalence and motoric subtypes of infant delirium in the ICU and describe obstacles to delirium assessment in this fragile population.

Methods: This was a single-center, prospective study in patients under 6-months of age admitted to the cardiac, medical-surgical ICU from December 2017 to June 2018. Enrolled patients were assessed daily for delirium while in the ICU using the Preschool Confusion Assessment Method for the ICU by the research team and independently by the psychiatry team using the Vanderbilt Assessment of Delirium in Infants and Children (VADIC). Challenges to assessment by the research and psychiatry teams were documented. Baseline demographics were obtained.

Results: We enrolled 53 critically ill patients aged 2 days - 6 months and performed 184 delirium assessments. Delirium prevalence was 41% with a rate of 61% in neonates (< 30 days of age) and 35% in patients aged 1–6 months. The majority of delirium assessments were of the hypoactive subtype (56%), versus the mixed subtype (33%) and hyperactive subtype (<1%). Delirium assessment was most challenging among premature infants and neonates. Lack of a developmental baseline was an issue for comparison assessment of delirium features such as a change in mental status. Age-related variance of the sleep wake cycle was pertinent to timing of arousal and attentive assessments, especially the postprandial physiologic state of restfulness that made arousing infants on cue difficult.

Conclusions: ICU delirium is prevalent in critically ill neonates and infants with hypoactive delirium the most common subtype. Accurate assessment of arousal states and attentiveness in this age group requires appreciation of variances in developmental processes and periods of normal and postprandial sleep. With recognition of these unique age-related challenges and using the bedside nurse to navigate timing of evaluations, delirium monitoring can be successful in this very young population.

ARE INFANTS IN THE NICU AT HIGHER RISK FOR DELIRIUM?

MANAGEMENT OF DELIRIUM

- Screen and monitor for signs and symptoms of delirium
- Identify and remove causative factors
- Environmental interventions by nursing and family
- Decrease deliriogenic medications like benzos, opiates
- Consider psychiatry consult and antipsychotic medications

CAPD

- Cornell Assessment of Pediatric Delirium
- It is an observational screening tool
- Assess critically ill children of all ages for delirium
- It has not been formally tested in a NICU population
- But has been validated in neonates and infants

Child with pediatric delirium.
Roel Seidell, with permission.

RASS Score _____ (if -4 or -5 do not proceed)

Please answer the following questions based on your interactions with the patient over the course of your shift:

	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0	Score
1. Does the child make eye contact with the caregiver?						
2. Are the child's actions purposeful?						
3. Is the child aware of his/her surroundings?						
4. Does the child communicate needs and wants?						
	Never 0	Rarely 1	Sometimes 2	Often 3	Always 4	
5. Is the child restless?						
6. Is the child inconsolable?						
7. Is the child underactive—very little movement while awake?						
8. Does it take the child a long time to respond to interactions?						
					TOTAL	

	NB	4 weeks	6 weeks	8 weeks	28 weeks	1 year	2 years
1. Does the child make eye contact with the caregiver?	Fixates on face	Holds gaze briefly Follows 90 degrees	Holds gaze	Follows moving object/caregiver past midline, regards examiner's hand holding object, focused attention	Holds gaze. Prefers primary parent. Looks at speaker	Holds gaze. Prefers primary parent. Looks at speaker	Holds gaze. Prefers primary parent. Looks at speaker
2. Are the child's actions purposeful?	Moves head to side, dominated by primitive reflexes	Reaches (with some discoordination)	Reaches	Symmetric movements, will passively grasp handed object	Reaches with coordinated smooth movement	Reaches and manipulates objects, tries to change position, if mobile may try to get up	Reaches and manipulates objects, tries to change position, if mobile may try to get up and walk
3. Is the child aware of his/her surroundings?	Calm awake time	Awake alert time Turns to primary caretaker's voice May turn to smell of primary care taker	Increasing awake alert time Turns to primary caretaker's voice May turn to smell of primary care taker	Facial brightening or smile in response to nodding head, frown to bell, coos	Strongly prefers mother, then other familiars. Differentiates between novel and familiar objects	Prefers primary parent, then other familiars, upset when separated from preferred care takers. Comforted by familiar objects especially favorite blanket or stuffed animal	Prefers primary parent, then other familiars, upset when separated from preferred care takers. Comforted by familiar objects especially favorite blanket or stuffed animal
4. Does the child communicate needs and wants?	Cries when hungry or uncomfortable	Cries when hungry or uncomfortable	Cries when hungry or uncomfortable	Cries when hungry or uncomfortable	Vocalizes /indicates about needs, e.g. hunger, discomfort, curiosity in objects, or surroundings	Uses single words, or signs	3-4 word sentences, or signs. May indicate toilet needs, calls self or me

	NB	4 weeks	6 weeks	8 weeks	28 weeks	1 year	2 years
5. Is the child restless?	No sustained awake alert state	No sustained calm state	No sustained calm state	No sustained calm state	No sustained calm state	No sustained calm state	No sustained calm state
6. Is the child inconsolable?	Not soothed by parental rocking, singing, feeding, comforting actions	Not soothed by parental rocking, singing, feeding, comforting actions	Not soothed by parental rocking, singing, feeding, comforting actions	Not soothed by parental rocking, singing, feeding, comforting actions	Not soothed by usual methods e.g. singing, holding, talking	Not soothed by usual methods e.g. singing, holding, talking, reading	Not soothed by usual methods e.g. singing, holding, talking, reading (May tantrum, but can organize)
7. Is the child underactive — very little movement while awake?	Little if any flexed and then relaxed state with primitive reflexes (Child should be sleeping comfortably most of the time)	Little if any reaching, kicking, grasping (still may be somewhat discoordinated)	Little if any reaching, kicking, grasping (may begin to be more coordinated)	Little if any purposive grasping, control of head and arm movements, such as pushing things that are noxious away	Little if any reaching, grasping, moving around in bed, pushing things away	Little if any play, efforts to sit up, pull up, and if mobile crawl or walk around	Little if any more elaborate play, efforts to sit up and move around, and if able to stand, walk, or jump
8. Does it take the child a long time to respond to interactions?	Not making sounds or reflexes active as expected (grasp, suck, moro)	Not making sounds or reflexes active as expected (grasp, suck, moro)	Not kicking or crying with noxious stimuli	Not cooing, smiling, or focusing gaze in response to interactions	Not babbling or smiling/laughing in social interactions (or even actively rejecting an interaction)	Not following simple directions. If verbal, not engaging in simple dialogue with words or jargon	Not following 1-2 step simple commands. If verbal, not engaging in more complex dialogue

CAPD SCORE >/= 9

- Evaluate for delirium
- Modify the environment
- Consider discontinuing medications that can cause delirium
- Treat underlying illness
- If it persistent, consider a trial of antipsychotic medications

ENVIRONMENTAL INTERVENTIONS

- Can prevent and help manage delirium in those that do need pharmacological treatment
- Establish daily routines and schedules
- Promote good sleep hygiene
- Control light and noise in the room
- Promote a familiar environment

PHARMACOLOGICAL MANAGEMENT

- Most importantly, decrease deliriogenic medications like benzos and opiate infusions
- Optimize pain and sedation while weaning benzo and opiate infusions
- Consider consulting clinical pharmacology
- Indications for considering antipsychotic medications
  - When the patient is distressed by the symptoms
  - The symptoms impose a safety concern/ device dislodgement
  - Or if symptoms are impeding advancement of medical care

ANTIPSYCHOTIC MEDICATIONS

Drug	Dosing	Forms Available	Frequencies of Adverse Effects[b]	Cardiac Effects[c]
Risperidone	Age 5–16 years, 0.5 mg–2.5 mg/day p.o., divided into two to four doses; maximum dosage: <20 kg, 1 mg/day, 20–45 kg, 2.5 mg/day, >45 kg, 3 mg/day	Oral (tablets, orally disintegrating tablets, solution), intramuscular (depot)	>30%: weight gain; >10%: sedation, agitation, extrapyramidal side effects (akathisia/parkinsonism > dystonia), anticholinergic effects, hyperglycemia, hyperlipidemia, orthostasis; <2%: skin reactions, blood dyscrasias,[d] seizures, hepatic impairment	Abnormal ECG, >2%; QTc prolongation, <2%; tachycardia, >10%
Olanzapine	Age 13–17 years, 2.5–10 mg/day; dosing every 12–24 hours; recommended maximum, 20 mg/day	Oral (tablets, orally disintegrating tablets), intramuscular	>30%: sedation, anticholinergic effects, weight gain, hyperlipidemia, hyperglycemia; >10%: insomnia, agitation; 2%–10%: extrapyramidal side effects (akathisia > dystonia/parkinsonism); >2%: orthostasis, hepatic impairment; <2%: skin reaction, blood dyscrasia, seizure	Abnormal ECG, <2%; QTc prolongation, <2%; tachycardia, <2%
Quetiapine	Age 10–17 years, 12.5–400 mg; dosing every 12–24 hours (usually 12 hours); recommended maximum, 750 mg/day	Oral (tablets; immediate release, extended release)	>30%: sedation, anticholinergic effects, hyperglycemia; >10%: agitation, orthostasis, weight gain, hyperlipidemia; >2%: extrapyramidal side effects (akathisia > parkinsonism/dystonia), hepatic impairment; <2%: seizure, skin reaction (no data for rate of blood dyscrasias with quetiapine[d])	Abnormal ECG, <2%; QTc prolongation, <2%; tachycardia, >2%

TAKE HOME POINTS

- Critically ill infants and children are at high risk for delirium
- PK of sedatives and analgesics in infants is different and contributes to increased risk
- Delirium is an under recognized clinical entity in the NICU
- Increased awareness of delirium as a differential and screening for it is critical
- Earlier identification and treatment can minimize associated morbidities and mortality

THANK YOU!

Questions?

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