Prematurity as a Risk Factor for ASD

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Disclaimer

We have no actual or potential conflicts of interest in relation to this program/presentation.

We will not discuss any investigational or off-label use of any drugs

Overview

Prematurity and its developmental sequelae

Long-term developmental follow-up studies

The ELGAN cohort and ASD risk

ASD screening recommendations and guidelines

ASD screening practices, tools

The "new generation" of screening tools

Prematurity and its Developmental Sequelae

Neurodevelopmental impairment is a significant long-term complication for survivors of prematurity:

- Risk increases with decreasing gestational age (GA) and birth weight (BW)

Challenges in interpreting outcome data:

- Differences in clinical practice
- Study design
- Changes in perinatal care

Prematurity: Defined

- World Health Organization (WHO)
  - Any birth before 37 completed weeks of gestation
- Preterm birth rates (United States, CDC 2015)
  - 1 out of 10 babies (10%) born preterm
  - Racial and ethnic differences in preterm birth rates
    - non-Hispanic black women (13%)
    - non-Hispanic white women (9%)

- Preterm Subcategories

Preterm definition	Completed weeks of gestation
Moderate to late preterm	32 to <37 weeks
Very preterm	28 to <32 weeks
Extremely preterm	< 28 weeks

Weight definition	Birth weight
Low birth weight	<2000 g
Very low birth weight	<1500 g
Extremely low birth weight	<1000 g

Neurodevelopmental and Behavioral Outcomes: Defined

Neurodevelopmental outcome:

- Composite term: cognitive, neurologic and/or sensory outcomes
- Long-term outcome arises from complex interplay of biologic, genetic, social and environmental factors
- Impairment defined as one or more of the following:
  - Cognitive delay
  - Moderate to severe cerebral palsy
  - Hearing deficit/loss requiring amplification
  - Severe visual impairment
  - Additional or shifting developmental dysfunction over time

Behavioral and psychological problems:

- Difficulties in attention
- Poor peer interaction
- Hyperactivity
- Emotional and conduct problems including anxiety, depression, withdrawn and somatic complaints
- Psychiatric disorders
- Autism spectrum disorders

Risk Factors for Neurodevelopmental and Behavioral Problems in the Preterm Infant

Prenatal

VLBW
GA <28 wks
IUGR
Male gender

Postnatal

Neonatal seizures
Abnormal HUS (IVH, white matter injury, PVL)
CLD, Prolonged mechanical vent
Infections (NEC, sepsis, meningitis)
Growth/Feeding problems
Extracorporeal membrane oxygenation
Low socioeconomic status
Maternal depression

Prevalence of Significant Disabilities in VLBW Infants/Children

Mental retardation	10-20%
Cerebral Palsy	5-21%
Blindness	2-11%
Deafness	1-3%
Motor delay	24%
Language problems	23-42%
ADHD	7-10%
Need for special education	9-28%
Psychological/behavioral problems	25%

Prematurity and Long-term Developmental Follow-up

- Prevalence of major neonatal morbidities remains largely unchanged
- Neurodevelopmental outcomes to 2-3 years (most centers) and through adolescence (various cohorts)
  - Cognitive impairment, IQ
  - Cerebral palsy
  - Sensory impairment
  - Neuropsychological outcomes
    - Cognitive processes and executive function
- Behavioral, social and emotional outcomes
  - Attention problems/ADHD
  - Increased rates of positive screens for ASD
  - "Behavioral phenotype" in extremely preterm infants (Johnson, et al., 2017)
    - Attention
    - Anxiety
    - Social difficulties

ASD Screening in Preterm Populations

Modified-Checklist for Autism in Toddlers *(M-CHAT/F; Robins et al., 1999),* a 23-item parent report measure for children 16-30 months old.

M-CHAT-Revised with Follow-Up *(M-CHAT-R/F; Robins et al., 2009).* 20-item measure.

- Some items require reasonably intact motor, vision and hearing
- Higher positive screening rates in preterm and low birth weight infants (21-41%)


1. Does your child enjoy being swung, bounced on your knee, etc.?
2. Does your child take an interest in other children?
3. Does your child like climbing on things, such as up stairs?
4. Does your child enjoy playing peek-a-boo/hide-and-seek?
5. Does your child ever pretend, for example, to talk on the phone or take care of dolls, or pretend other things?
6. Does your child ever use his/her index finger to point, to ask for something?
7. Does your child ever use his/her index finger to point, to indicate interest in something?
8. Can your child play properly with small toys (e.g. cars or bricks) without just mouthing, fiddling, or dropping them?
9. Does your child ever bring objects over to you (parent) to show you something?
10. Does your child look you in the eye for more than a second or two?
11. Does your child ever seem oversensitive to noise? (e.g., plugging ears)
12. Does your child smile in response to your face or your smile?
13. Does your child imitate you? (e.g., you make a face-will your child imitate it?)
14. Does your child respond to his/her name when you call?
15. If you point at a toy across the room, does your child look at it?
16. Does your child walk?
17. Does your child look at things you are looking at?
18. Does your child make unusual finger movements near his/her face?
19. Does your child try to attract your attention to his/her own activity?
20. Have you ever wondered if your child is deaf?
21. Does your child understand what people say?
22. Does your child sometimes stare at nothing or wander with no purpose?
23. Does your child look at your face to check your reaction when faced with something unfamiliar?

Prematurity and ASD Screening: ELGAN 1 Study

Extremely Low Gestational Age Newborns (ELGAN Study)

- Multi-center observational cohort study of <28 weeks GA infants born between 2002-2004
- Designed to identify characteristics and exposures that increase the risk of neurologic disorders
- 14 sites, including Yale

Positive Screening on M-CHAT in ELGANs (Kuban et al., 2010)

- 21% of ELGANs screened positive for ASD on the M-CHAT (n=988)
  - Positive M-CHAT screen associated with motor, neurosensory, and neurocognitive impairment
  - 16% without motor or sensory impairment
  - 10% without cognitive impairment
- Possibility of low specificity of M-CHAT in preterms due to associated developmental impairments and other characteristics

Prematurity and ASD Screening and Diagnosis: ELGAN 2

ELGAN and risk factors for ASD at 10 years (Joseph et al. , 2016)

- 3.2% ASD without intellectual disability
- 3.8% ASD with intellectual disability
- 23-24 week gestation associated with highest risk of ASD (OR 2.9-4.4)
- Severe fetal growth restriction (OR 9.9)

Predictive Validity of the Modified Checklist for Autism in Toddlers (M-CHAT) Born Very Preterm (Kim et al., 2016)

- M-CHAT at 24 months in relation to diagnosis of ASD at age 10 (n=863)

Sensitivity	52%
Specificity	84%
PPV	20%
NPV	96%

- >50% not correctly screened by M-CHAT at 2 years
- High false positive and false negative rates with hearing/visual impairments
- High false positive rates associated with
  - Lower SES
  - Motor and cognitive impairments
  - Emotional/behavioral dysregulation

Prematurity and ASD Screening: ELGAN 1 and 2

- ASD Screening Measure
  - M-CHAT in extremely preterm population had lower sensitivity and PPV than expected
    - Demographic factors
    - Cognitive
    - Sensorimotor
    - Emotional/behavioral dysregulation
- Recommendations
  - Use standard M-CHAT criteria with caution
  - Utilize follow-up interviews (M-CHAT R/F)
  - Need to consider supplementing with other screening measures given impact of these factors on misclassification rates

Timing of First Concerns about ASD vs. Diagnosis

Up to 50% of parents of children with ASD report having concerns in the first 12 months; most by age 2 (Chawarska et al., 2007)

Average age of diagnosis of ASD in U.S.: 4 ½ years (Baio et al., 2014)

Downward trend: 2002 median age = 5.6 years; 2010 = 4.4 years

Delay between symptom onset and diagnosis: 2 to 3 years

Primary care pediatricians: critical to identifying delays and ASD in very young children

Gaps can be reduced by screening

Screening and Surveillance: Key Terms

Developmental screening*:* administration of standardized tools, often completed by parents.

- Ages and Stages Questionnaires (ASQ); Child Development Inventories (CDI); Parents' Evaluations of Developmental Status (PEDS)

ASD-specific screening**:** administration of standardized tools, often completed by parents.

- M-CHAT (Modified Checklist for Autism in Toddlers)

Developmental surveillance: eliciting parental concerns, documenting a longitudinal developmental history, observing child, identifying risk factors, maintaining an accurate record, including obtaining input from others

Current Recommendations & Guidelines

American Academy of Pediatrics (2006, 2007, 2010, 2014-16):

2-stage screening for ASD (18 & 24 months) or anytime a concern is raised, in addition to developmental surveillance at every well-child visit and developmental screening at 9, 18, 24/30 months

American Academy of Child and Adolescent Psychiatry (1999, 2014):

Developmental/psychiatric assessment of young children should routinely include questions about ASD symptomatology

CDC: Same as AAP; additional developmental screening if child is at high risk (e.g., *sibling with ASD,* ***preterm birth****, low birthweight*)

Current ASD Screening Practices

Trend: increase in screening for ASD

- 8% (2006) ; 28% (2009)
- 50% at 24-month visit, 60% at 18-month visit (2012)

More than half of toddlers identified with significant ASD symptoms were found through screening BEFORE pediatricians or parents were concerned (2000 - 2013)

Screening outperforms surveillance

- RCT: Earlier identification of delays, earlier referral to EI, earlier eligibility for EI services (2013)
- 67% of infants with developmental delays missed based on pediatricians' clinical observation alone (2007)
- Only some toddlers with significant ASD symptoms identified by screening were already of concern to parents or pediatricians (2011)
- Toddlers screened for ASD were referred and diagnosed earlier (2011)

ASD Screening Instruments

- Single-measure
- Developmentally sensitive
- Developmentally sensitive *and* accounts for heterogeneity

ASD Screening Instruments: Single Measure

Modified-Checklist for Autism in Toddlers *(M-CHAT/F; Robins et al., 1999),* M-CHAT-Revised with Follow-Up *(M-CHAT-R/F; Robins et al., 2009).* For children 16-30 months old.

Positive predictive value:

- When follow-up questions used, ~50% of screen-positives were diagnosed with ASD
- 95% had an actionable developmental concern *(Chlebowski al., 2013; Robins et al., 2014)*

Negative predictive value:

- Norwegian population study of M-CHAT (without follow-up) administered at 18 months: 2/3 of children later diagnosed with ASD *were missed (Stenberg et al., 2014)*

M-CHAT Screening in Premature Children

- Issues
  - M-CHAT in extremely preterm population had lower sensitivity and PPV than expected (Kim et al., 2016)
- Recommendations
  - Utilize follow-up interviews (M-CHAT R/F)
  - Need to consider other screening measures given impact of various factors on misclassification rates
  - Refer for in-depth evaluation at clinics specializing in developmental disabilities

ASD Screening Instruments: Developmentally-Sensitive

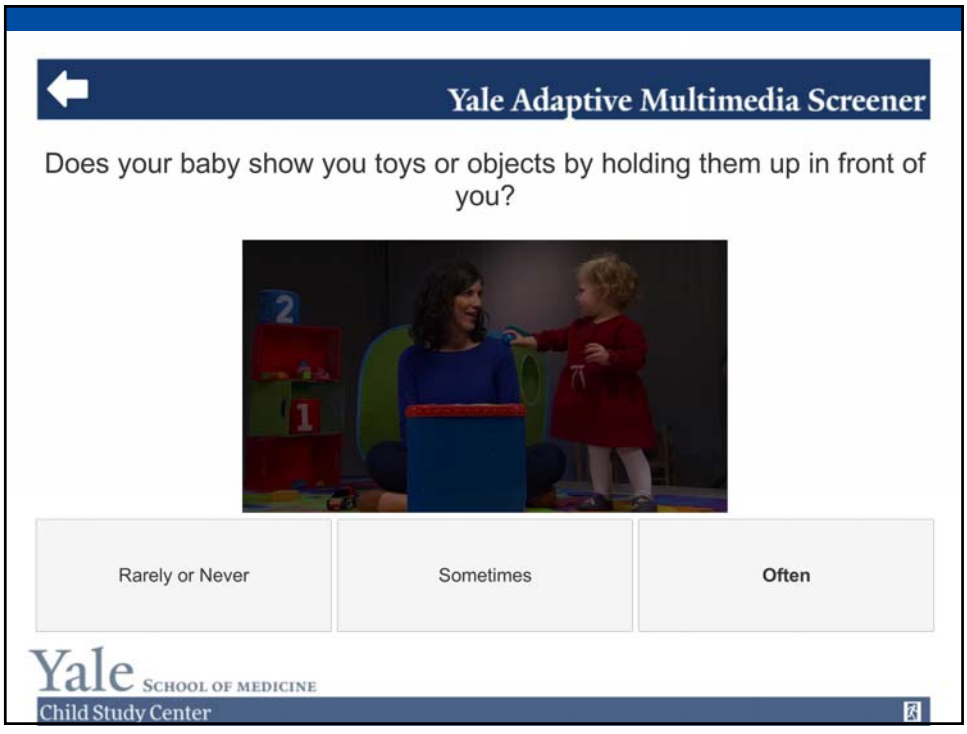
- Communication and Symbolic Behavior Scales-Infant Toddler Checklist (CSBS-ITC) *(Wetherby et al., 2008)*
  - Age-normed broadband screener
  - Focus on social & communication skills
  - Utility for ASD screening (2008, 2011)

Limitations of ASD Screeners

- Properties
  - sensitivity/NPV
  - specificity/PPV
- Content and format
  - Some developmental knowledge required
  - Concepts can be difficult to describe in words
  - Yes-no format
- Administration
  - Need to be scored
  - Follow-up interview extends visit

Yale Adaptive Multimedia Screener

- Multimedia
- Tablet-based



Summary and Conclusions

- Infants affected by specific prenatal or neonatal events such as prematurity, VLBW, and small for gestational age are at increased risk for ASD
- Each additional week of gestational age decreases the risk of ASD
- Independent of gestational age, SGA was associated with increased ASD risk
- Mechanisms: it is unclear if factors associated with ASD are causal or merely indicators of lower physiological maturity
- M-CHAT, though the best-studied ASD screener, does not perform well in these populations
- These infants should be referred to specialized early evaluation clinics for diagnostic clarification
- New screeners are currently in development

Thank you!

http://www.cdc.gov/ncbddd/actearly/index.html
http://www.cdc.gov/ncbddd/childdevelopment/screening-hcp.html
www.mchatscreen.com
www.m-chat.org
http://www.brookespublishing.com/resource-center/screening-and-assessment/csbs/csbs-dp/csbs-dp-itc/