Autism spectrum disorder & congenital CMV

MORE THAN JUST A COINCIDENCE

Samantha Nikirk, MPH

Megan Pesch, MD

Disclosures

- Nikirk: National CMV Foundation
- Pesch: Consultant for Moderna, MedScape/WebMD, National CMV Foundation, Funding from NICHD and Gerber Foundation

Introductions

Learning objectives

1) Summarize the **current research** on the associated between congenital CMV and increased risk of autism spectrum disorder
2) Understand the **challenges of diagnosing** children with co-occurring autism and congenital CMV, and to advocate for an evaluation
3) Discuss the **unique developmental strengths and weaknesses** in children with co-occurring congenital CMV and ASD, and strategies of support for them and their families.

What is autism spectrum disorder?

- **'a lifelong developmental disability that affects how people perceive the world and interact with others'**
  - NAS, 2019

- **'a neurological difference meaning the individual perceives the world differently. This can include senses and communication (in- and outgoing)'**
  - Krysia Waldock, 2016/2019

DSM-V – medical diagnosis

A. **Persistent deficits in social communication and social interaction**

i) **Deficits in** social-emotional reciprocity

ii) **Deficits** nonverbal communicative behaviors used for social interaction

iii) **Deficits** in developing, maintaining, and understand relationships

B. **Restricted, repetitive patterns of behavior, interests, or activities**,

i) Stereotyped or repetitive motor movements, use of objects, or speech

ii) Insistence on sameness, inflexible adherence to routines

iii) Highly restricted, fixated interests

iv) Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment

The Spectrum

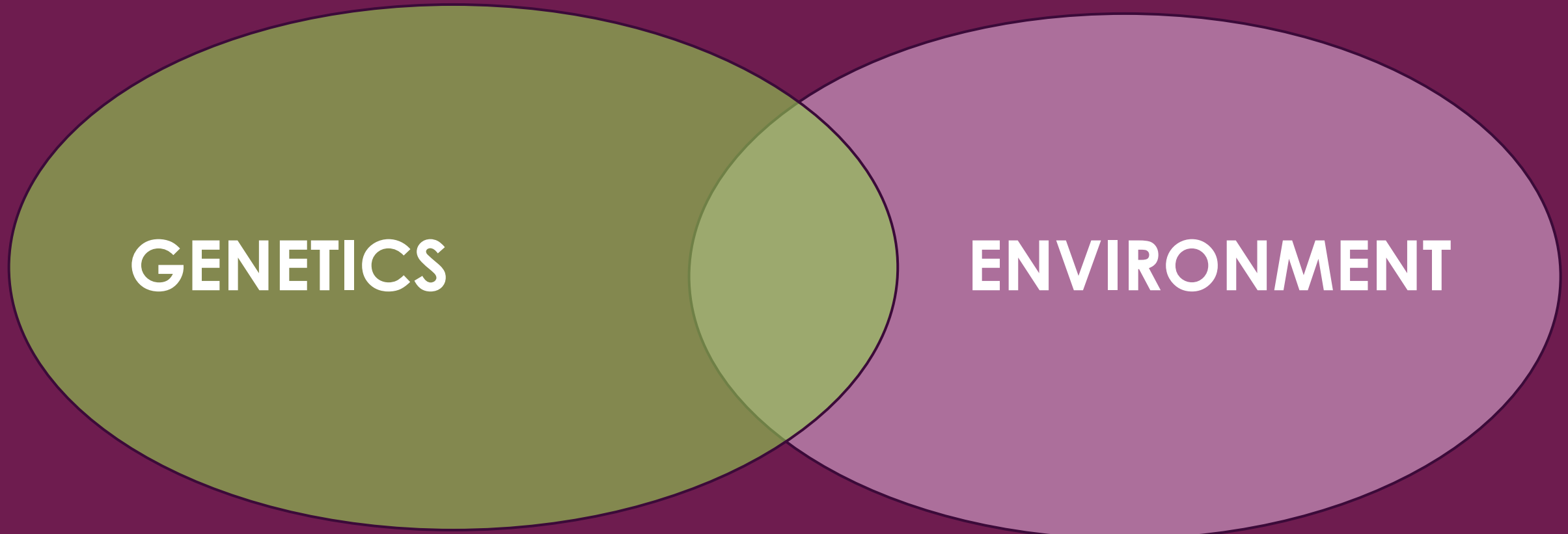
Not a line and not prescriptive
Like a mixing board

NEURODIVERSITY

Differences in a person's brain which means they may experience the world differently

Exploring Diagnosis and University of Exeter, 2018

What causes autism?

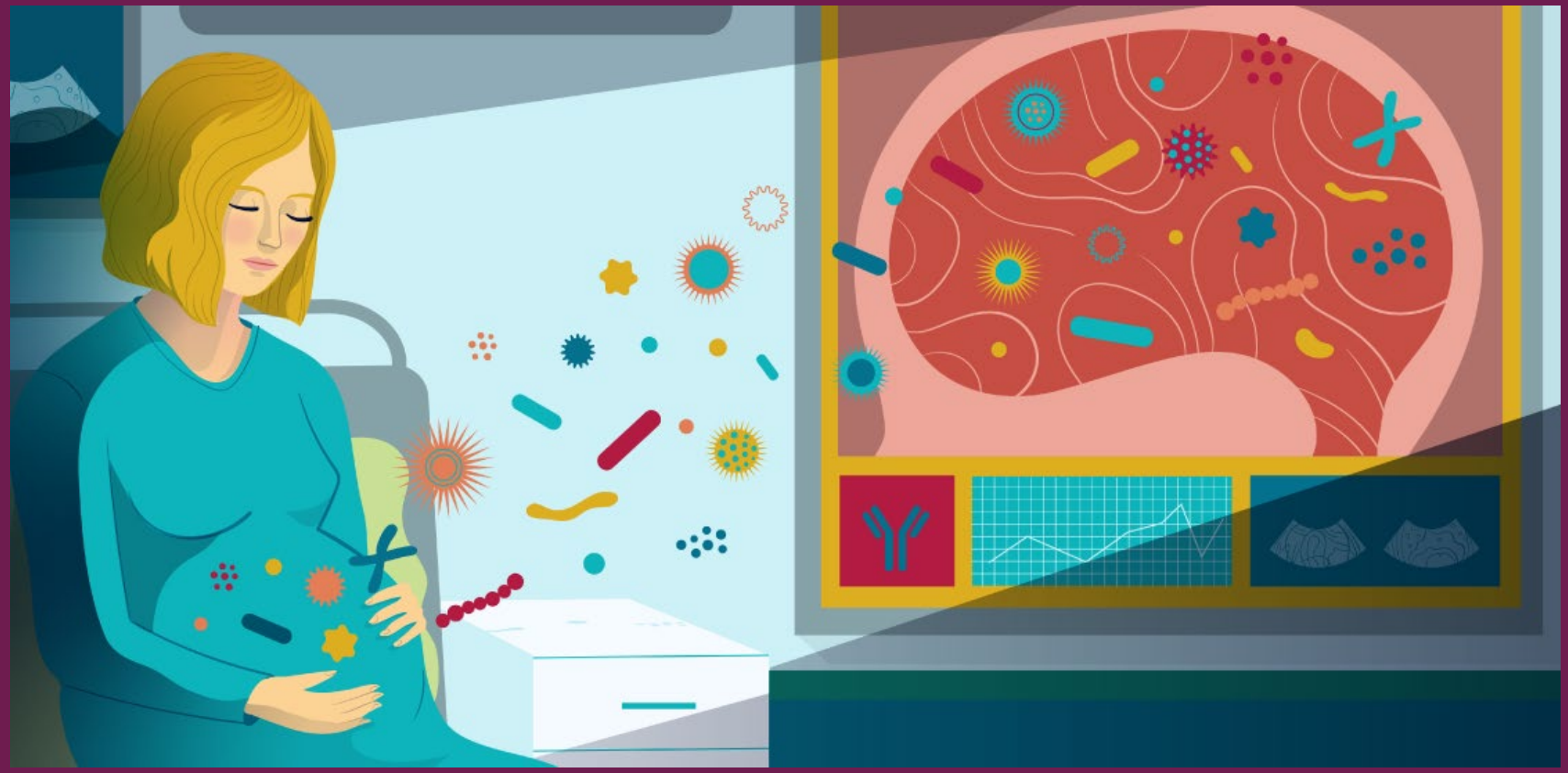


Huguet, Guillaume, and Thomas Bourgeron. "Genetic causes of autism spectrum disorders." In *Neuronal and synaptic dysfunction in autism spectrum disorder and intellectual disability*, pp. 13-24. Academic Press, 2016.

Autism is not caused by

https://www.thetreetop.com/aba-therapy/what-causes-autism

Congenital infections and autism risk



Congenital infections and autism risk

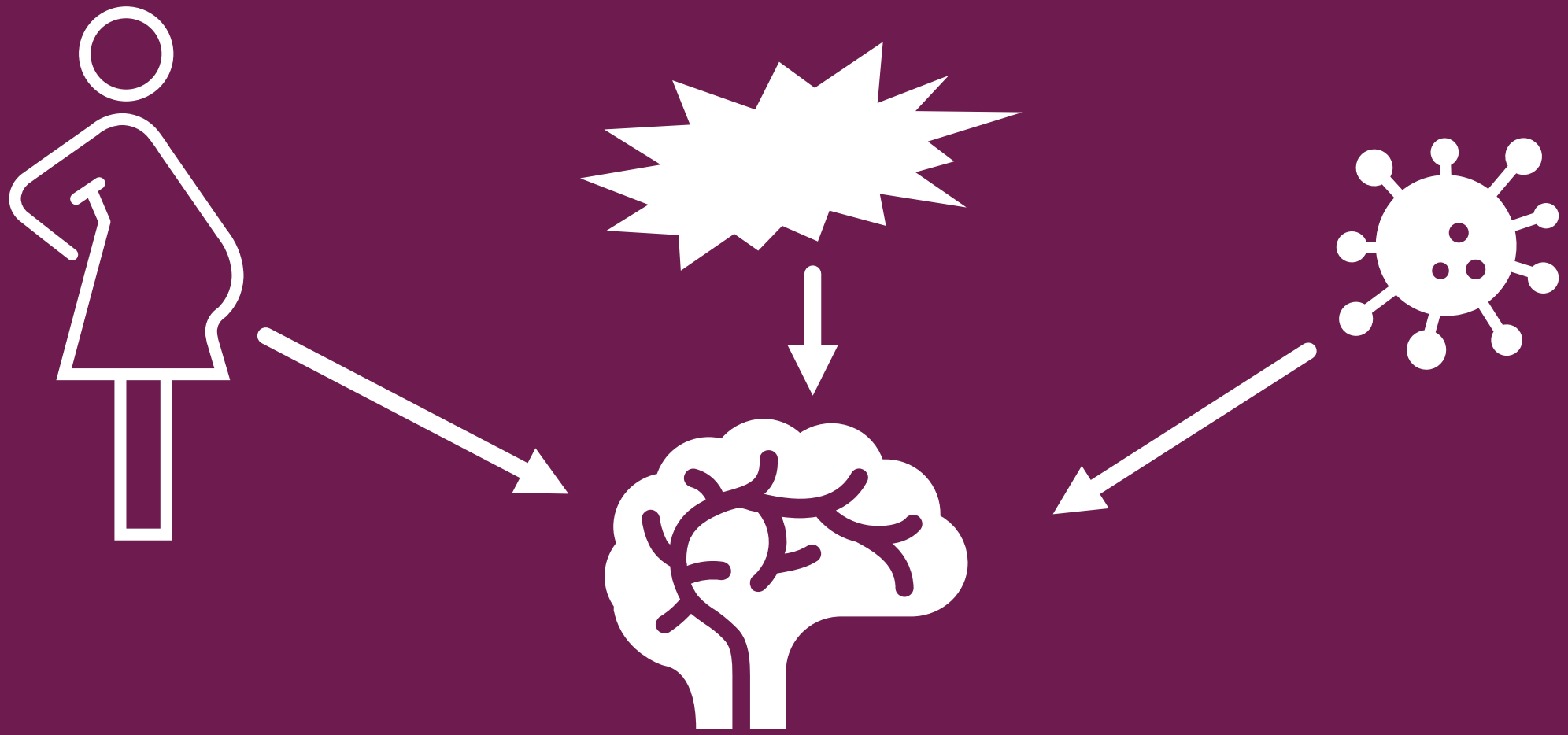
- Congenital rubella infections 1960's
- Hospitalization with infection in pregnancy → 37% increased chance of child with ASD
- Fever in 2nd trimester → 40% ↑
- Viral infections (influenza, rubella etc)

Lee BK, Magnusson C, Gardner RM, Blomström Å, Newschaffer CJ, Burstyn I, Karlsson H, Dalman C. Maternal hospitalization with infection during pregnancy and risk of autism spectrum disorders. Brain Behav Immun. 2015 Feb;44:100-5. doi: 10.1016/j.bbi.2014.09.001. Epub 2014 Sep 16. PMID: 25218900; PMCID: PMC4418173..

Hornig M, Bresnahan MA, Che X, Schultz AF, Ukaigwe JE, Eddy ML, Hirtz D, Gunnes N, Lie KK, Magnus P, Mjaaland S, Reichborn-Kjennerud T, Schjølberg S, Øyen AS, Levin B, Susser ES, Stoltenberg C, Lipkin WI. Prenatal fever and autism risk. Mol Psychiatry. 2018 Mar;23(3):759-766. doi: 10.1038/mp.2017.119. Epub 2017 Jun 13. PMID: 28607458; PMCID: PMC5822459.

Shuid AN, Jayusman PA, Shuid N, Ismail J, Kamal Nor N, Mohamed IN. Association between Viral Infections and Risk of Autistic Disorder: An Overview. Int J Environ Res Public Health. 2021 Mar 10;18(6):2817. doi: 10.3390/ijerph18062817. PMID: 33802042; PMCID: PMC7999368.

How could congenital infections increase the risk of autism?



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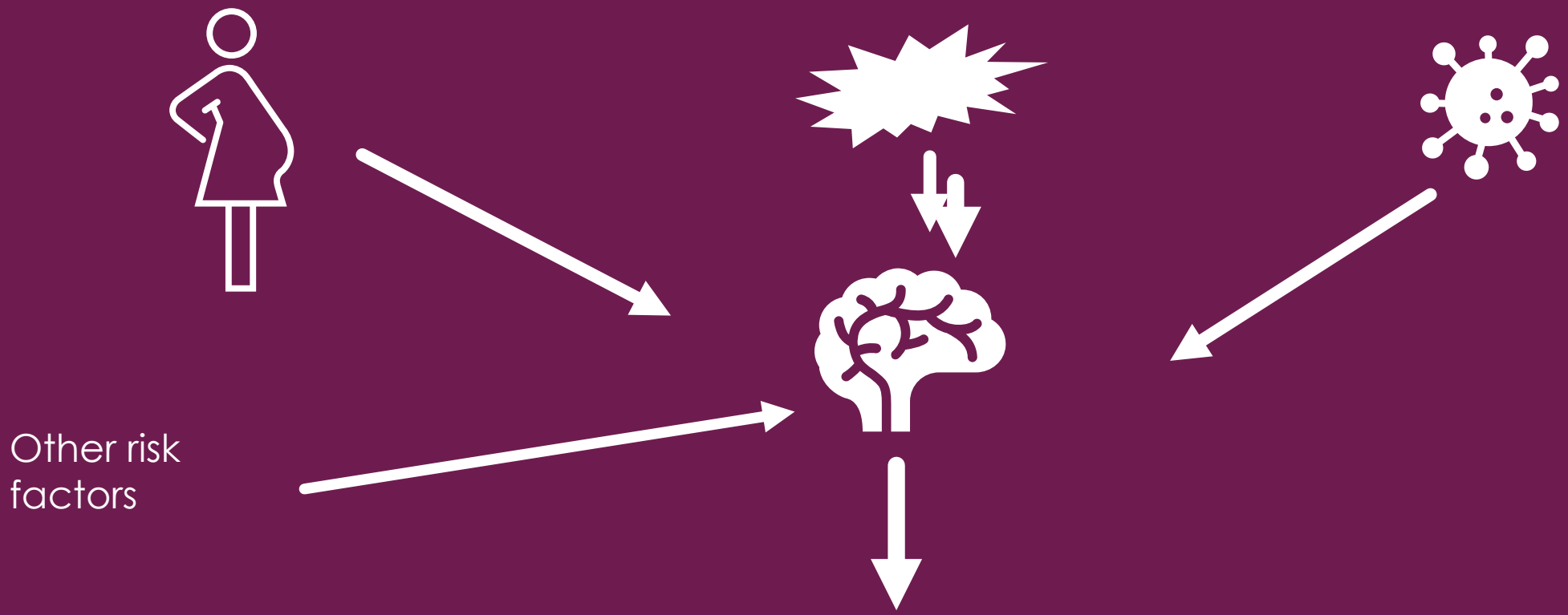
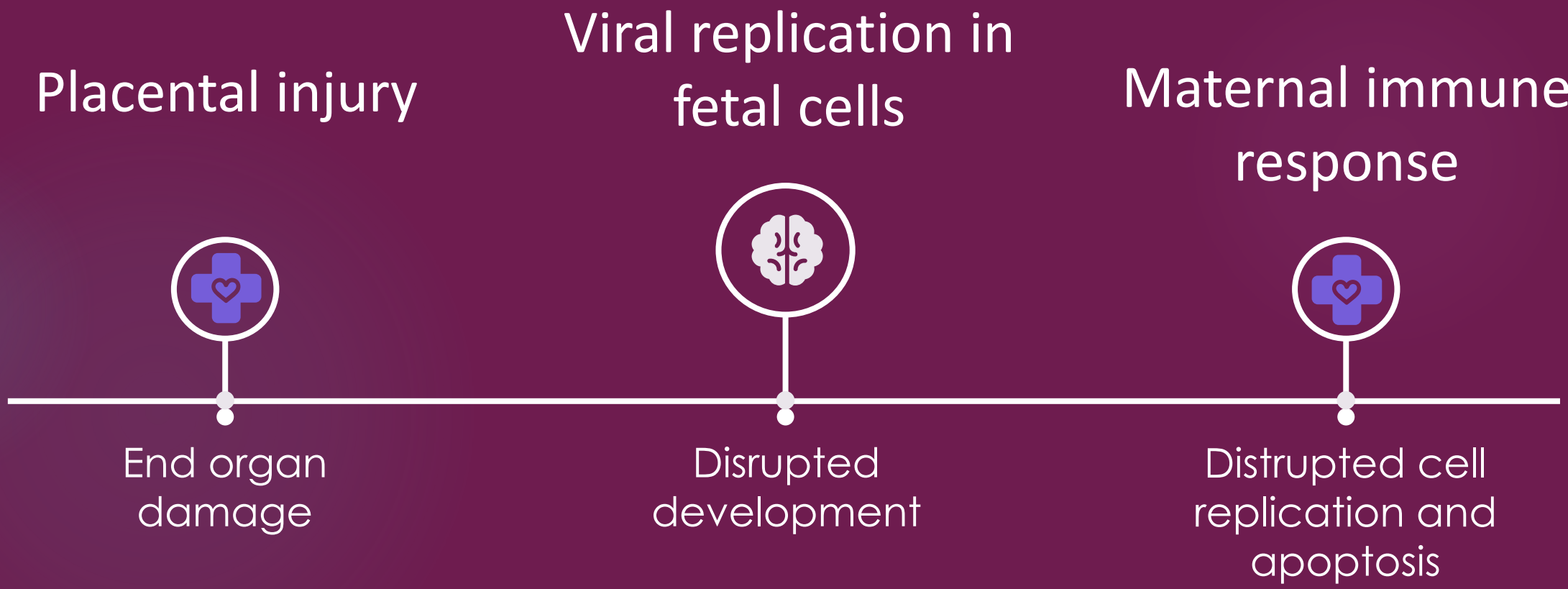
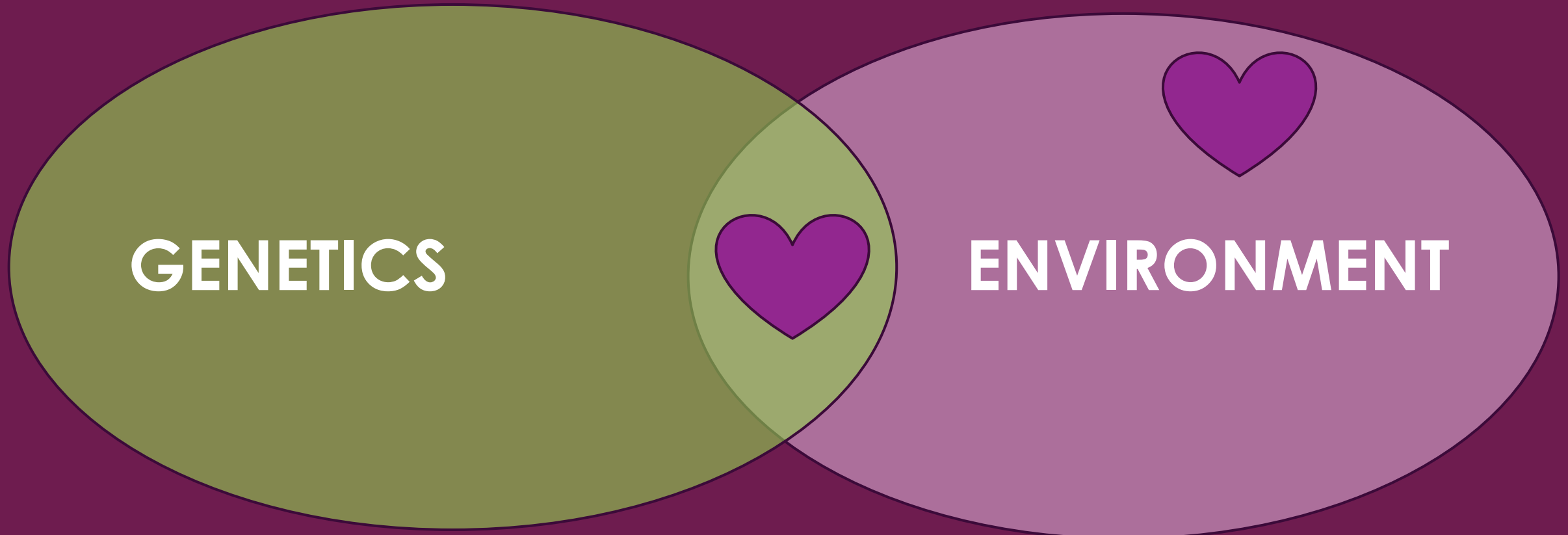


Mechanisms of fetal injury



Krstanović F, Britt WJ, Jonjić S, Brizić I. Cytomegalovirus Infection and Inflammation in Developing Brain. Viruses. 2021 Jun;13(6):1078.

What causes autism?



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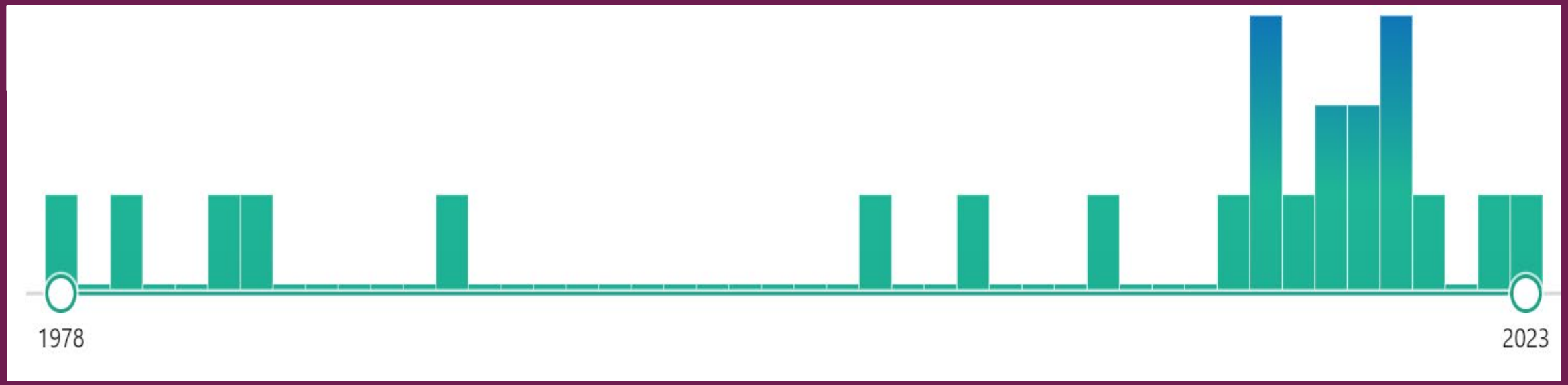
Is there a link between autism and congenital CMV?

Current literature

- Pub Med search: “autism” and “congenital cytomegalovirus”
- 19 studies



Types and number of studies

- Case reports (1-2 children) = 5 studies
- Other articles (reviews, economic valuations) = 6
- Small sample of kids with ASD (<40) = 3
- Small sample of kids with CMV (<40) = 4
- Population level study = 1

Keymeulen et al, 2023

- Flemish CMV registry
- CMV + Neurodevelopmental outcomes reported
- N= 753
- 70% with “normal” outcomes, 30% with sequelae
- ASD reported in 2.5% vs. 0.7% in general population

Keymeulen A, De Leenheer E, Casaer A, Cossey V, Laroche S, Mahieu L, Oostra A, Van Mol C, Dhooge I, Smets K. Neurodevelopmental outcome in children with congenital cytomegalovirus infection: A prospective multicenter cohort study. Early Human Development. 2023 Jul 1;182:105777.

cCMV Development and Behavior Study

- Survey study to assess the developmental and behavioral outcomes of children diagnosed with cCMV
- Caregiver/parent respondents
- Eligibility Criteria:
  - Children with suspected or confirmed cCMV
  - Ages 1 – 10
  - English
- Instruments selected based on age group
  - 1 – 3 years of age
  - 4 – 10 years of age

CCMV Development and Behavior Study Preliminary results

	1-3 years of age (N=29)	4-10 years of age (N=17)
Symptomatic	24	16
Asymptomatic with hearing loss	3	0
Asymptomatic	2	1
Female	14	10
Hearing Loss	19	9

Modified Checklist for Autism in Toddlers (M-CHAT)

- Autism screening tool for toddlers (16 – 30 months)
- 20 question test (yes/no) that parents/caregivers can complete
- Looks for multiple signs of autism and assesses **risk level**
  - High Risk Score: 8 – 20
    - Refer for early intervention and diagnostic assessment
  - Medium Risk Score: 3 – 7
    - Complete additional follow-up, refer for diagnostics if behaviors continue
  - Low Risk Score: 0 – 2
    - No follow-up needed

M-CHAT Results

- N = 29; ages 1 – 3

MCHAT Score Category	N =	Autism Diagnosis N =
Low Risk (0-2)	11	0
Moderate Risk (3-7)	6	0
High Risk (8-20)	12	5

Social Communication Questionnaire (SCQ)

- Autism screening tool (Age 4 plus)
- 40-item questionnaire (yes/no response)
- Parent/Caregiver report screening of symptoms associated with autism
- Looks for multiple signs of autism and assesses **risk level**
  - High Risk Score: > 11
    - Refer for early intervention and diagnostic assessment
  - Low Risk Score: ≤ 11

SCQ Results

- N = 17; ages 4 – 10

SCQ Score Category	N=	Autism Diagnosis N =
High Risk (>11)	6	0
Low Risk (≤ 11)	11	1

Anecdotal vs Literature Reported

VS

Why the discrepancy?

- cCMV under diagnosed
- Lack of central registries
- cCMV testing not part of routine ASD evaluation
- Symptomatic vs asymptomatic

Challenges in diagnosing autism in children with congenital CMV

(and vice versa)

Hearing loss & ASD

- 2-3 per 1000 US newborns have hearing loss[1]
- 1/59 children with ASD have hearing loss
- Why?
  - Related syndromes (e.g. Down Syndrome)
  - Common risk factors (e.g. infection)
  - ASD children may have different responses to sensory input

Centers for Disease Control and Prevention (CDC). Identifying infants with hearing loss - United States, 1999-2007. MMWR Morb Mortal Wkly Rep. 59(8): 220-223. Vohr B. Overview: infants and children with hearing loss—part I. Ment Retard Dev Disabil Res Rev. 2003;9:62–64.

Diagnostic challenges

- Lots of overlap in presentation
- Risk of delayed diagnoses
- AAP recommend children with ASD → hearing eval
- Children with certain disabilities need specialized behavioral testing to evaluate for ASD

Hearing loss or ASD?

- Child does not make eye contact when name called
- Child has speech and language delay
- Child takes person's hand to indicate wants or needs
- Does not communicate through facial expression
- Child insists on sameness,
- Child is strongly routine based
- Avoids certain lights, smells, sounds, or textures
- Reduced sharing of interests', joint attention
- Does not have age-appropriate play or friendships

Diagnostic challenges

- Limited instruments validated for children with disabilities
- Modified scoring (ADOS and ADIR)
- Careful assessment, multidisciplinary if possible

Fazzi E, Micheletti S, Galli J, Rossi A, Gitti F, Molinaro A. Autism in children with cerebral and peripheral visual impairment: fact or artifact?. InSeminars in pediatric neurology 2019 Oct 1 (Vol. 31, pp. 57-67). WB Saunders.
Williams ME, Fink C, Zamora I, Borchert M. Autism assessment in children with optic nerve hypoplasia and other vision impairments. Developmental Medicine & Child Neurology. 2014 Jan;56(1):66-72.

How to support children with autism and cCMV

Benefits of having an autism diagnosis

- Eligibility for more services
- Tailored supports
- Better understanding of child as an individual
- Respect → pride

Challenges of some children with autism

- May misread social cues or facial expressions
- Social interactions/group work may be stressful
- Stress-relieving activities may make others uncomfortable
- Sensory perceptions can interfere with learning
- Nebulous sense of time (can impact multi-tasking)
- Difficulty with changes and transitions

Strengths of some children with autism

- “Out of the box” thinkers
- Intelligent
- Reliable (once expectations are understood)
- Strong attention to detail
- Ability to maintain prolonged focus on topics of interest
- Excellent long-term and rote memory

Clinical consideration for ASD+CMV

- Sensory experiences heightened
- Anxiety heightened
- Bodily autonomy
- Communication, communication, communication
- Build social communication foundation first

Autism “treatments” – Applied Behavioral Analysis

- <60s - people with developmental or intellectual disabilities were commonly institutionalized
- ABA developed by Ole Ivar Lovaas in the 60s to “make people with autism “normal”
- ”Viewed as shifting the paradigm from “hopeless to treatable”
- One-size-fits-all approach

Applied Behavioral Analysis

- **Increase "positive behaviors":**
  - Language, self-help, play, communication, social skills, academic, reading, motor-skill
- **Decrease maladaptive behaviors:**
  - Aggression, self-stimulatory behaviors, self-injury
- May be more "adapted" to societal expectations??

The problem with traditional ABA

- ABA is founded on an underlying goal of making children with autism "normal" or to fit into society easier but that is not necessarily the goal of the recipients
- Aversive "therapy" used to deter behaviors
- "The emphasis should be on learning to function in areas the individual chooses, not on changing who she is."

Newer “ABA”

- Insurance coverage = all billed as “ABA”
- Social skills building
- Speech therapy – AAC device - ASL
- Functional goals
- What is underlying the behavior?

Newer “ABA”

- **Younger kids**
  - Play based, naturalistic, involving parents, personalized goals
- **Older kids**
  - Social skills groups, working on flexibility, rigid behaviors, personalized

ABA red flags

- Food as a reward
- Token economies
- Compliance focused
- Sitting at table → flash cards
- 40 hours a week

Summary

- Congenital infections increase risk of autism
- Neurodiversity is a beautiful thing
- Anecdotal vs research evidence
- Diagnosing ASD in children with cCMV can be challenging
- Interventions → Respectful, skill focused, individualized

THANK YOU