Children's Hospital LOS ANGELES
We Treat Kids Better

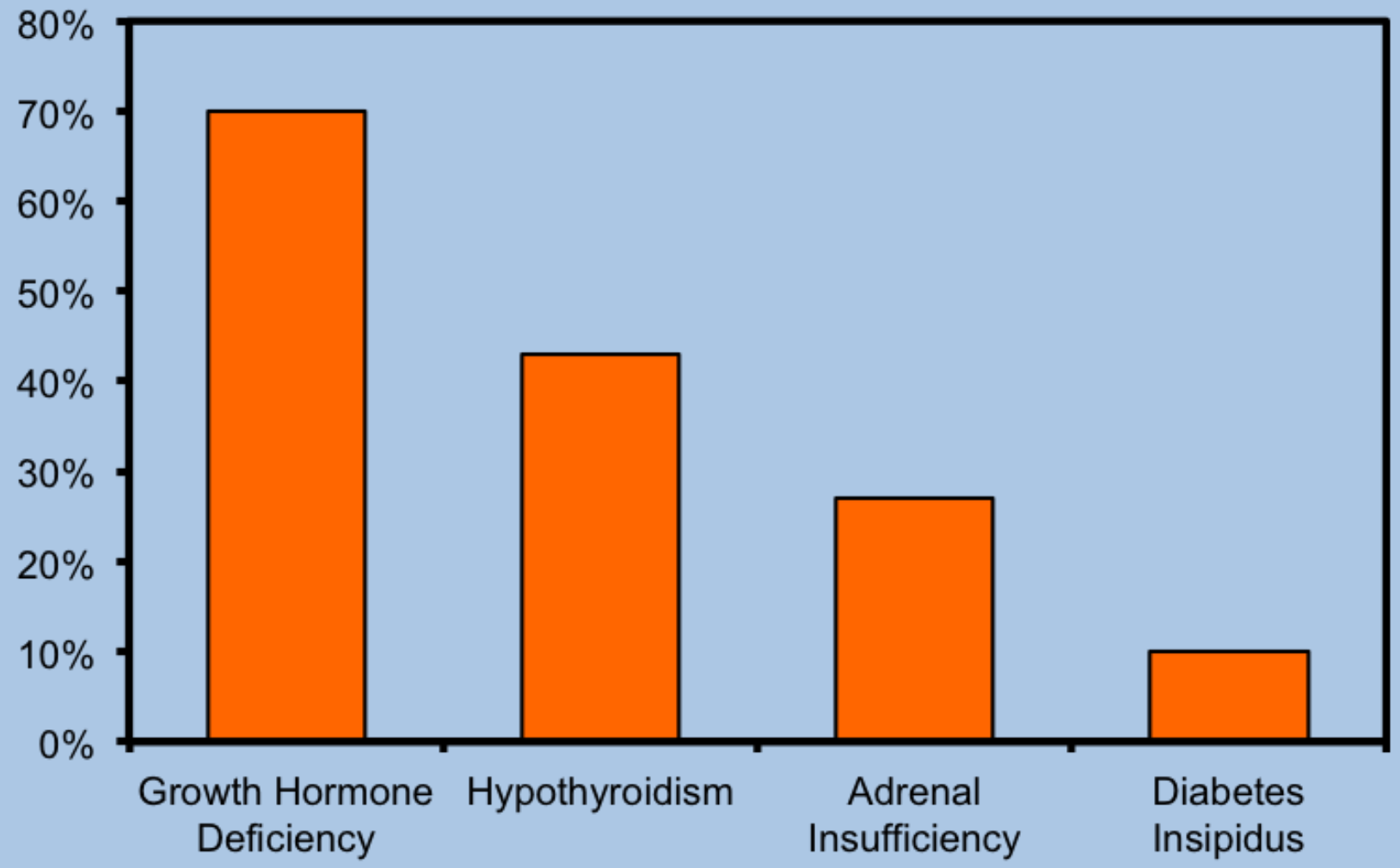
USC UNIVERSITY OF SOUTHERN CALIFORNIA

Optic Nerve Hypoplasia
Part 2:
Clinical Problems

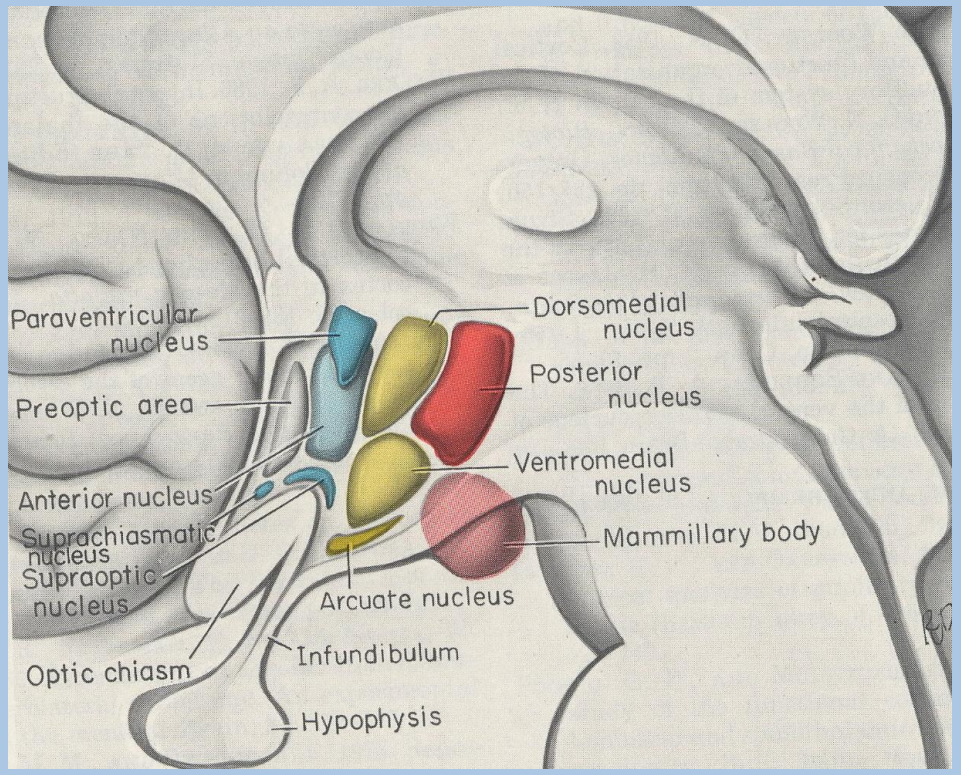
Hypopituitarism

- Deficiencies in:
  - Growth hormone
  - Thyroid hormone
  - ACTH (cortisol)
  - Anti-diuretic hormone (diabetes insipidus)
  - Sex hormones

Frequency of Pituitary Hormone Deficiencies in Children with ONH



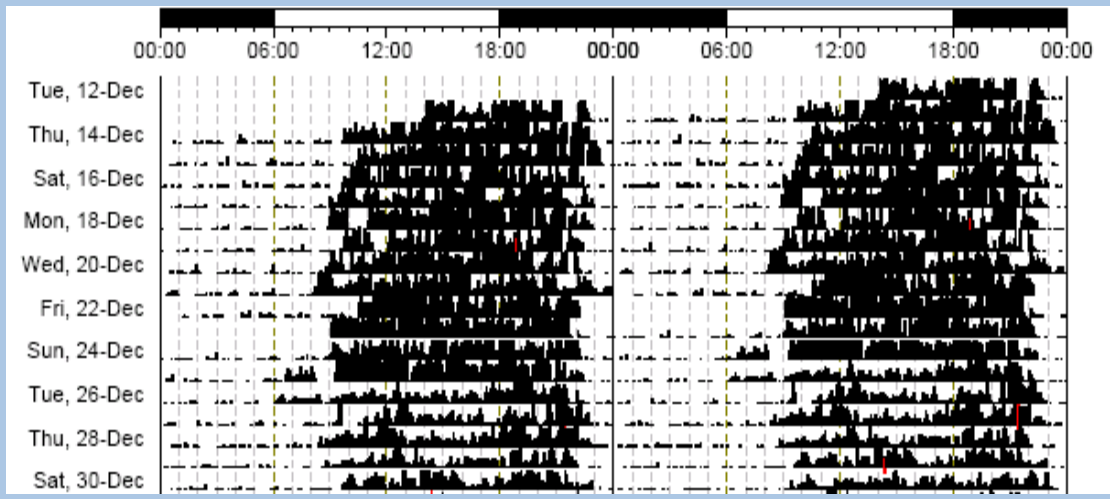
Hypothalamic Dysfunction: Sleep



<u>Suprachiasmatic Nucleus</u>:

- **Located in hypothalamus**
- **Controls sleep rhythm**

Actigraphy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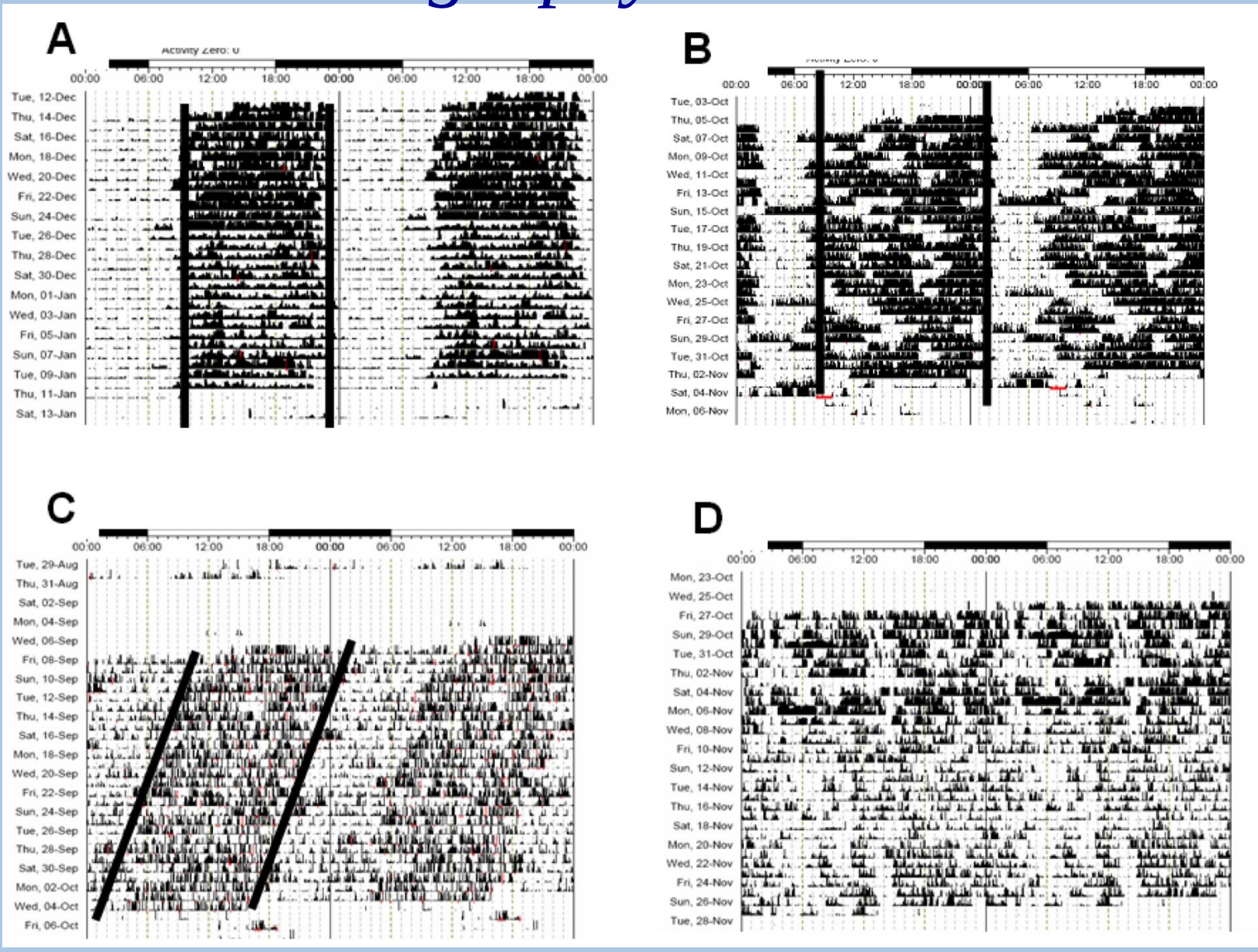
Actigraphy in ONH



Clinical Associations with Sleep

	Normal rest-activity	Abnormal rest-activity	P-value
# Subjects	13	6	
Age (mos.)	44	40	0.45
Vision score	1.7	4.7	**.006**
Normal pupils	85%	17%	.008
CC hypoplasia	30%	66%	0.18
≥1 hormone def.	53%	66%	>0.17
≥2 hormone def.	30%	66%	0.11
≥3 hormone def.	7%	66%	**.03**
Dev. delay	15%	100%	**.04**

Sleep Dysfunction

- 30% of ONH patients have abnormal rest activity
- Disruptive to family
- Abnormal rest-activity correlates:
  - Worse vision
  - ≥ 3 hormone deficits
  - Severe developmental delay

Growth and Obesity

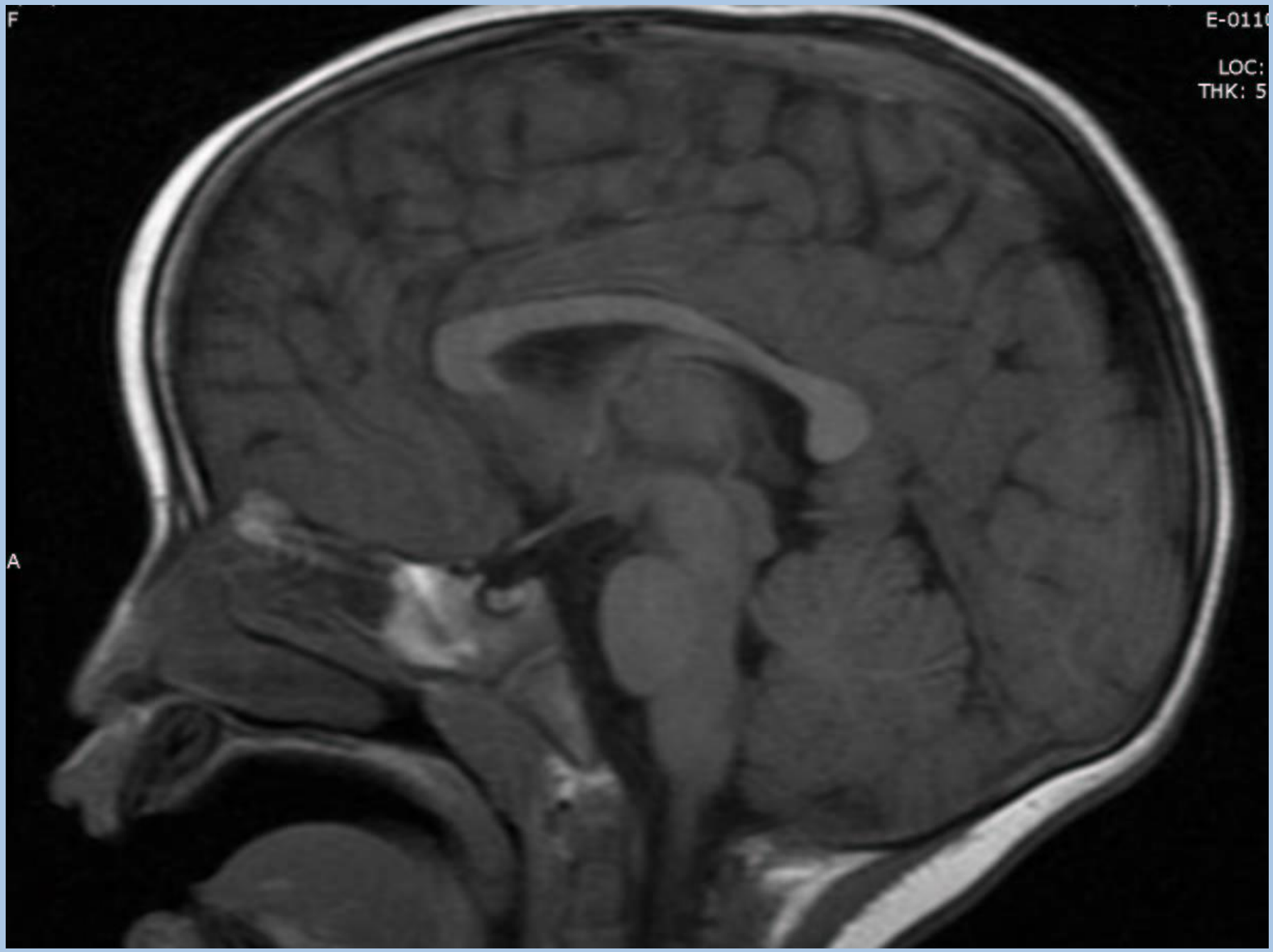
- May grow normally with GH deficiency until age 6 years
- 44% children with ONH and GHD are obese
- Children with ONH respond better to GH treatment than those with congenital GHD
- Early GH treatment has no effect on obesity and minimal beneficial effect on body composition and lipid profile

MRI Findings & Developmental Delay

- Septum Pellucidum
  - 72% delayed if absent (vs. 73%)

✓ Corpus Callosum
  - 96% delayed if hypoplastic (vs. 58%)

✓ Other major malformations
  - 100% delayed if present (vs. 68%)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Corpus Callosum and Developmental Disorders

- Corpus callosum area measurements much smaller in subjects with delay
- Increased risk of cognitive impairment - 2.7 (1.4-5.8) for each cm^2 decrement in corpus callosum area

Laterality & Developmental Delay

- Unilateral cases (18%)
  - 38.5% have developmental delay
- Bilateral cases (82%)
  - 78.3% have developmental delay

Endocrine Dysfunction & Developmental Delay

Any endocrine dysfunction

- ✓73.6% delayed (vs. 60% without dysfunction)

Hypothyroidism

- ✓93% delayed (vs. 51% with normal levels)

Hypothyroidism in ONH

- Central hypothyroidism detected in ONH at mean age of 15 mos.
- Hypothyroidism is major risk factor for cognitive impairment in ONH
- Hypothyroidism can evolve
- Vision outcomes better in subjects without hypothyroidism

History of ONH & Autism

- Recent recognition
- Increasing prevalence
- Similar incidence trajectories
- Overlapping symptoms & signs

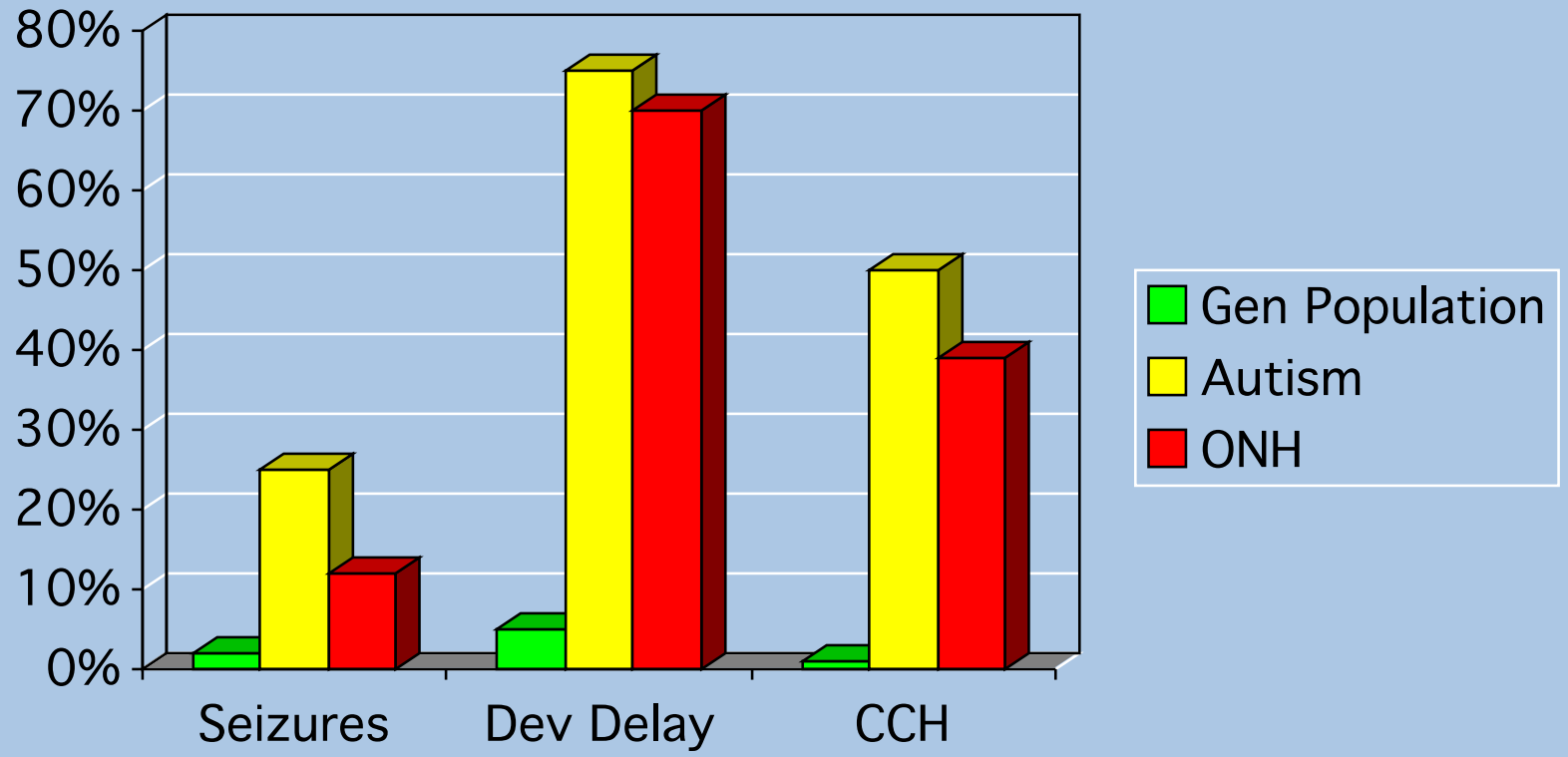
Autism Behaviors Noted in ONH

- Rigid
- Dependence on Routines
- Lack of spontaneity in verbal interactions
- Perseverative behavior
- Tactile & auditory defensiveness

ONH & Autism Similarities

- Developmental delay
- Seizures
- Gastrointestinal dysfunction
- Sleep disturbance
- Corpus Callosum hypoplasia
- Accelerated head circumference growth
- Neonatal jaundice

Clinical Characteristics



Autism noted in ONH

- Margalith (1984) - 21% of children with ONH had dev impairment including autism
- Ek (2005) - 46% of ONH & blindness had diagnosis of autism
- Parr (2010) - 31% of ONH with clinical autism diagnosis
- Miller (2004) - 10-15% of other congenital ocular anomalies with autism
- CDC (2010) - 0.9% General population

Developmental Milestones (months)

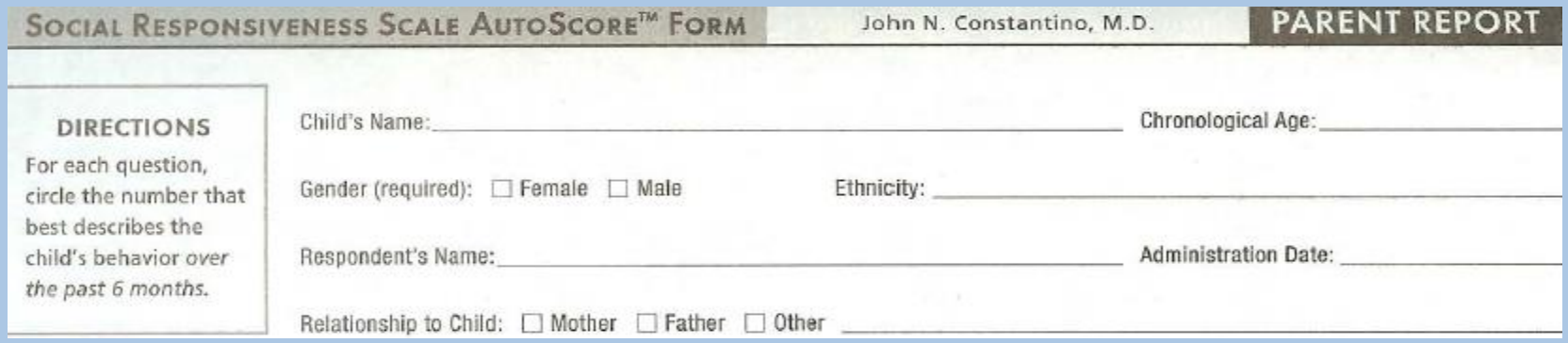
Milestone	Norm	VI Only	VI +Autism
Reaches/Touches Object	5.4	8.1	10.6
Sits alone	6.6	9.2	11.9
Crawls 3ft	9	11.4	18.3
Plays interactive game	9.7	9.3	13.1
Walks w/o support	13	19	26.6
Follows direction	20.5	19.3	25
Relates past experiences	40	36.9	37.7

Question: Is this really autism?

- Inexperience by examiners with visually-impaired children
- Behavior attributable to VI, neurological impairment, social-emotional deprivation
- Problems with diagnostic tools

Problem with Diagnostic Tools

- Highly visually-dependent joint attention behaviors (eye contact, referential eye gaze and pointing)
- Repetitive behaviors normal in blind children (rocking)
- Language abnormalities normal in blind children (pronoun reversal)
- Orienting behaviors normal in blind children (smelling, touching)



SOCIAL RESPONSIVENESS SCALE AUTOSCORE™ FORM John N. Constantino, M.D. PARENT REPORT

DIRECTIONS

For each question, circle the number that best describes the child's behavior *over the past 6 months.*

Child's Name: _____ Chronological Age: _____

Gender (required): ☐ Female ☐ Male Ethnicity: _____

Respondent's Name: _____ Administration Date: _____

Relationship to Child: ☐ Mother ☐ Father ☐ Other _____

2. Expressions on his or her face don't match what he or she is saying.

9. Clings to adults, seems too dependent on them.

15. Is able to understand the meaning of other people's tone of voice and facial expressions.

16. Avoids eye contact or has unusual eye contact.

21. Is able to imitate others' actions.

45. Focuses his or her attention to where others are looking or listening.

55. Knows when he or she is too close to someone or is invading someone's space.

65. Stares or gazes off into space.

Social Communication Questionnaire (SCQ)

9. Has her/his facial expression usually seemed appropriate to the particular situation?

10. Has she/he ever used your hand like a tool or as if it were part of her/his own body (e.g. pointing with your finger)?

22. When she/he was 4 to 5 did she/he ever spontaneously point at things around her/him just to show you things?

26. When she/he was 4 to 5 did she/he usually look at you directly in the face when doing things with you or talking with you?

27. When she/he was 4 to 5, did she/he smile back if someone smiled at her/him?

Autism Diagnostic Observation Schedule

- ADOS is dependent on level of functioning- different modules depending on level of language.
- For less verbal children, activities rely on free and structured play.
- Informal modifications have been used- enlarging pictures, using larger toys with more tactile interest.

Research at CHLA

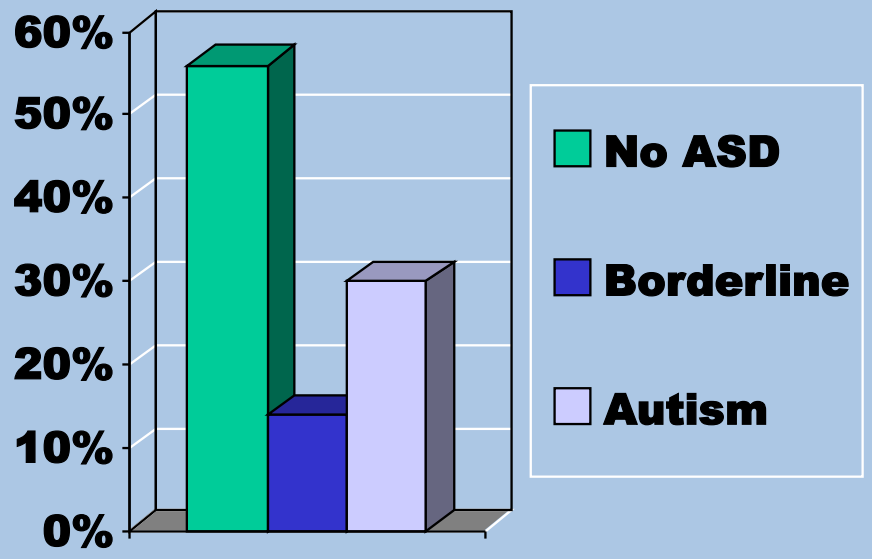
- Pilot study

→ ASD screening assessment added to prospective study

  - Objective: Assess level of ASD
  - Social-responsiveness scale (SRS)*
    - performed at final study visit (age 5)

**modified for visual impairments*

Social Responsiveness Scale-Results



- 5/37 (13%) scored at the level of high-functioning ASD.
- 11/37 (30%) scored at the level of autism.

Clinical Characteristics Associated with SRS

	High SRS	Low SRS
Corpus Callosum Hypoplasia	73%	40%
Seizures	36%	5%
Final Vision	Motion perception	20/80
Developmental Delay	90%	4.8%

CHLA Study Autism Evaluations

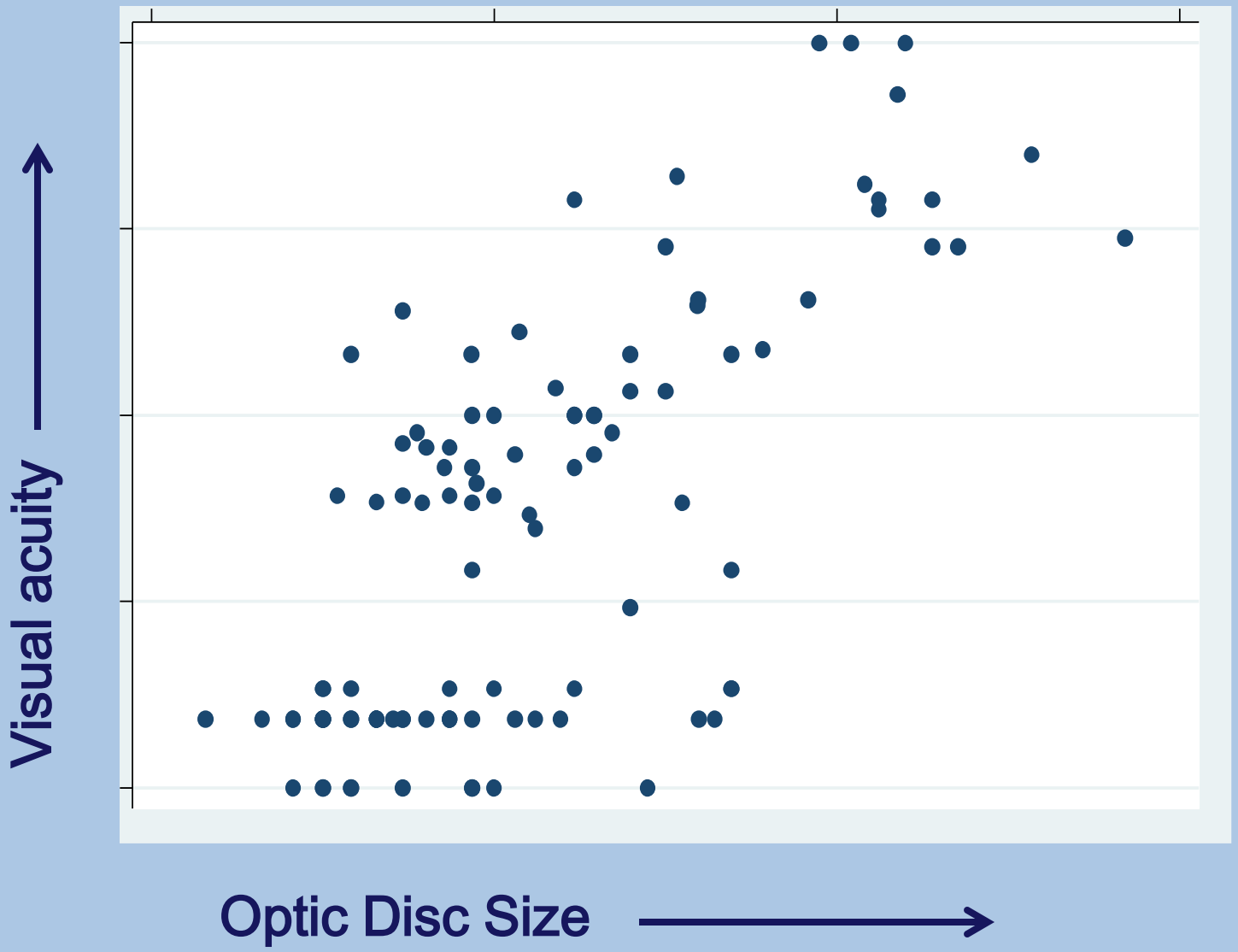
- Aim: Modify existing ASD screening and diagnostic tools for use independent of vision.
- Evaluate participants (with and without signs of autism on the SRS) using the ADI-R and ADOS modified for vision impairment by two masked experts.

Autism in ONH

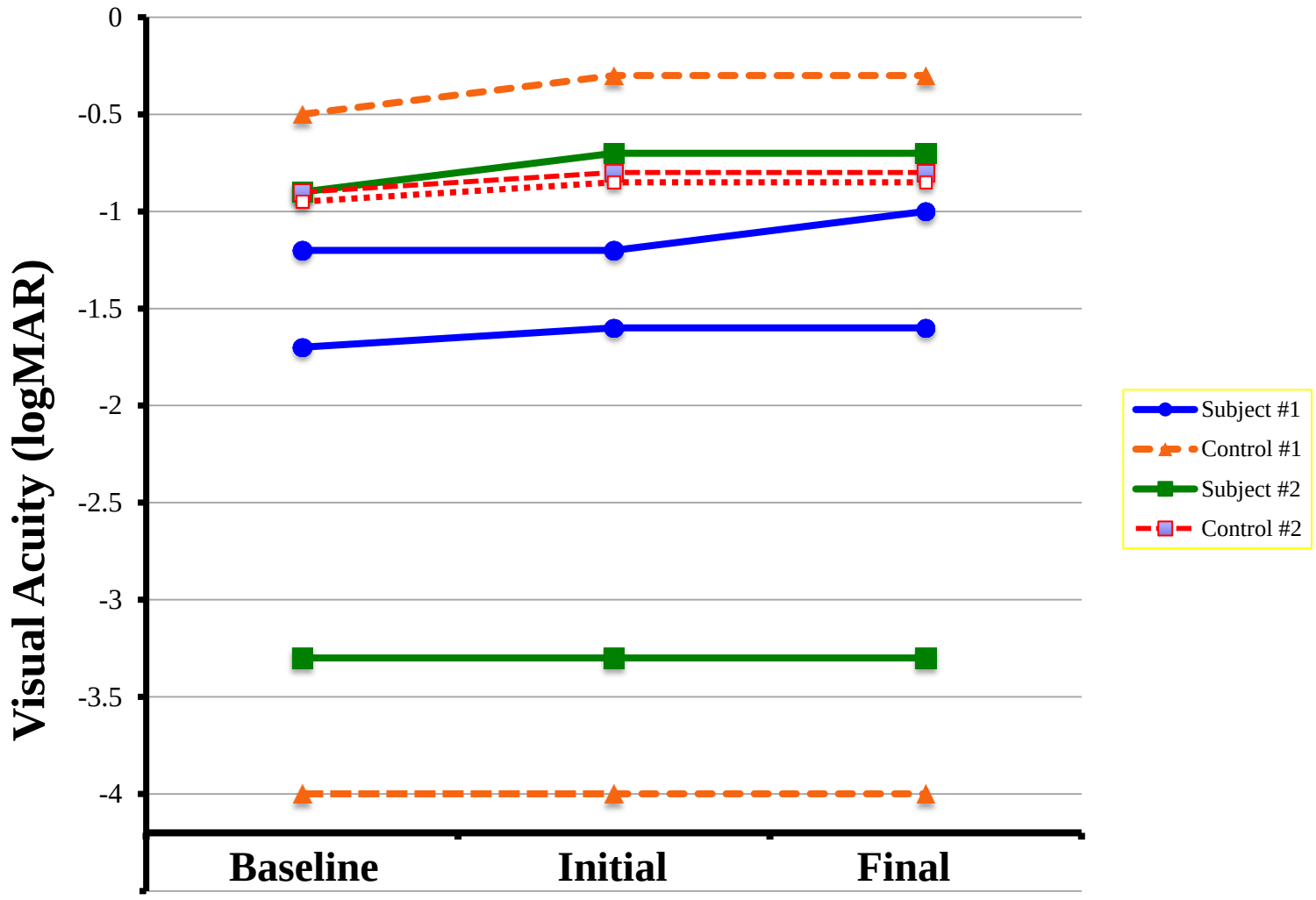
- Modified ADOS is sensitive and specific for ASD in blind children
- Modified ADI-R is less reliable
- Poor correlation with modified SRS
- Good correlation with modified SCQ
- Prevalence of autism in ONH and other causes of VI still needs to be determined

Vision in ONH

- Visual behavior improves in most cases
- Vision outcome correlates with:
  - pERG amplitude (RGCs, amacrine cells
  - flash VEP amplitude (optic nerve, visual cortex
  - optic disc size
  - optic disc pallor


Visual acuity
Optic Disc Size

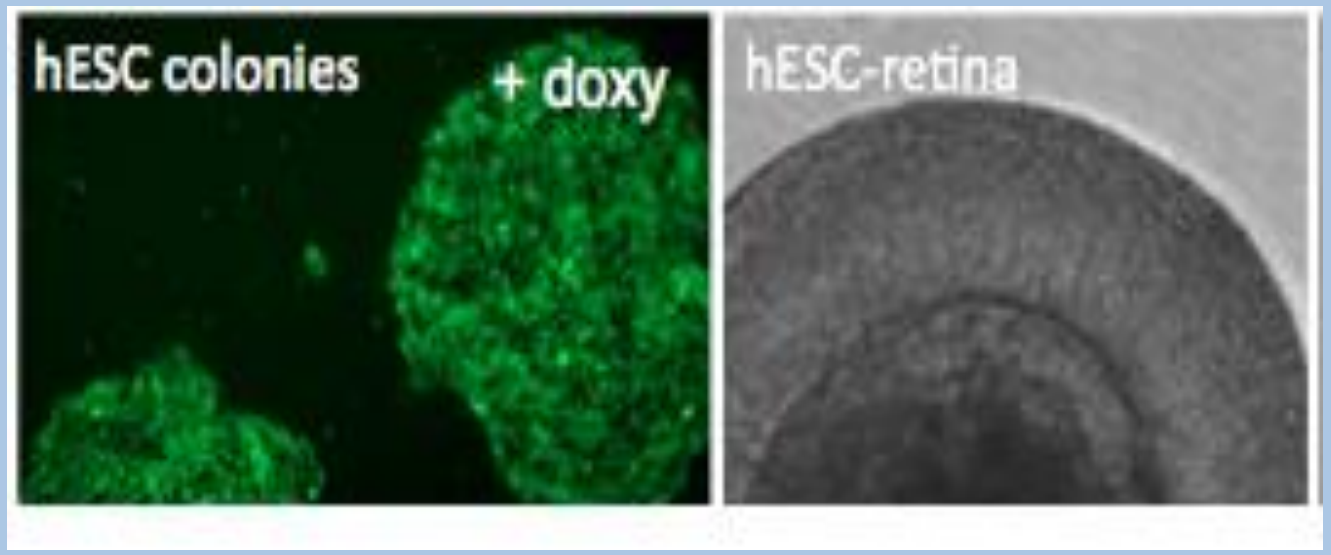
Effect of CBSC Infusion on VA



Vision in ONH

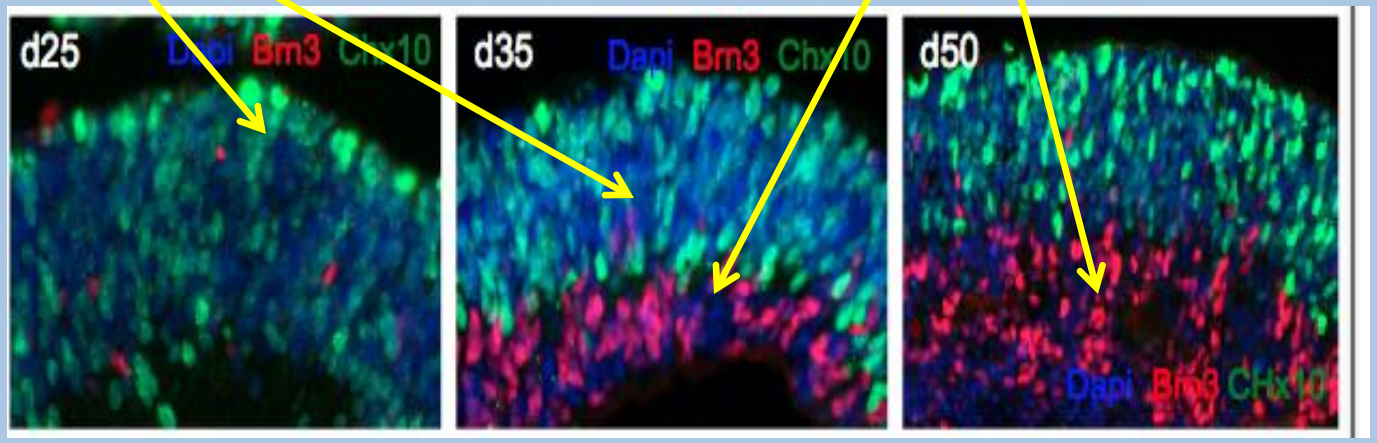
- Relationship to pVEP, pERG, optic disc size suggests related to optic nerve potential
- Improvement in VA corresponds with period of optic nerve myelination
- Improvement mirrors that of CVI
- Suggests improvement in ONH may be actually related to CVI, but limited by ONH potential

Embryonic Retinas from Stem Cells



RPCs

RGCs



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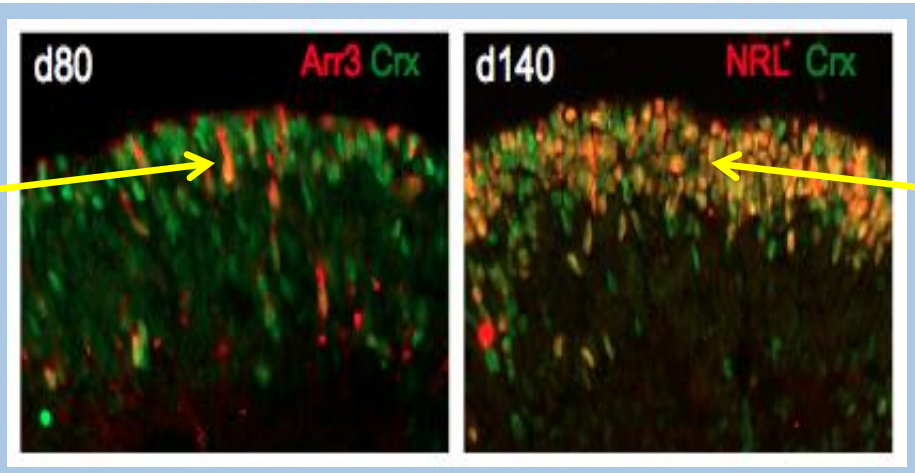

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Conclusions

ONH is the hallmark of a congenital syndrome manifested by:

- Poor vision in one or both eyes
- Hypothalamic dysfunction
- Developmental delay
- Various neuro-radiographic abnormalities

Conclusions

- ONH is a spectrum condition in which brain malformations and hypopituitarism are independent manifestations
- “Septo-optic dysplasia” is a misleading and historically inaccurate term
- Developmental delay may be related to brain malformations or hypothyroidism

Conclusions

- Vision improvement in ONH may be related to CVI
- Powerful new laboratory techniques hold potential for understanding and treatment of ONH