Autism in the First Years of Life

Eric Courchesne and Karen Pierce
UC San Diego
Autism Center of Excellence

Dedicated to the memory of Gail Courchesne, loving mother and gifted musician
RED FLAGS of Autism Spectrum Disorder by 12-24 Months

**Reduced social interest and affect**
- lack of warm, joyful emotional expressions
- lack of sharing emotional enjoyment or interest
- lack of response to name
- lack of showing and interacting

**Abnormal language development**

Lack of coordination of gaze, facial expression, gesture & sound during interactions
The Prospective Study of Autism

1 Yr Well-Baby Check-Up Approach

- Fast
- Easy
- Investigates autism as it occurs in the population

Karen Pierce et al., 2011
J. Pediatrics
CSBS DP Infant-Toddler Checklist

Social Communication Composite

Expressive Speech Composite

Symbolic Composite

Emotion and Eye Gaze
1. Do you know when your child is happy and when your child is upset? □ Not Yet □ Sometimes □ Often
2. When your child plays with toys, does he/she look at you to see if you are watching? □ Not Yet □ Sometimes □ Often
3. Does your child smile or laugh while looking at you? □ Not Yet □ Sometimes □ Often
4. When you look at and point to a toy across the room, does your child look at it? □ Not Yet □ Sometimes □ Often

Communication
5. Does your child let you know that he/she needs help finding an object out of reach? □ Not Yet □ Sometimes □ Often
6. When your child is not paying attention to you, does he/she try to get your attention? □ Not Yet □ Sometimes □ Often
7. Does your child do things just to get your attention? □ Not Yet □ Sometimes □ Often
8. Does your child try to get you to notice interesting objects—just to get you to look at the objects, not to get you to do anything with them? □ Not Yet □ Sometimes □ Often

Gestures
9. Does your child pick up objects and give them to you? □ Not Yet □ Sometimes □ Often
10. Does your child show objects to you without giving you the object? □ Not Yet □ Sometimes □ Often
11. Does your child wave to greet people? □ Not Yet □ Sometimes □ Often
12. Does your child point to objects? □ Not Yet □ Sometimes □ Often
13. Does your child roll her/his head to indicate yes? □ Not Yet □ Sometimes □ Often

Sounds
14. Does your child use sounds or words to get what he/she wants? □ Not Yet □ Sometimes □ Often
15. Does your child string sounds together, such as da-da, ma-ma, ga-ga, eye-eye, baba? □ Not Yet □ Sometimes □ Often
16. About how many of the following consonant sounds can your child use: ma, na, ba, da, go, wo, ya, ya, yah? □ 1-2 □ 3-4 □ 5-8 □ over 8

Words
17. About how many different words does your child use meaningfully that you recognize (such as baby for bottle; gaggie for doggie)? □ None □ 1-3 □ 4-10 □ 11-30 □ over 30
18. Does your child put two words together (for example, more cookie, bye bye, the) □ Not Yet □ Sometimes □ Often

Object Use
19. When you call your child’s name, does he/she respond by looking or turning toward you? □ Not Yet □ Sometimes □ Often
20. About how many different words or phrases does your child understand without gestures? For example, if you say “where’s your tummy,” “where’s Daddy,” “give me the ball,” or “come here,” without showing or pointing, your child will respond □ None □ 1-3 □ 4-10 □ 11-30 □ over 30

Social Communication Composite

Expressive Speech Composite

Symbolic Composite
Dr. Robert Bjork, Dr. Michael Nelson, Dr. Cheryl Jennett
Dr. Dr. John Kafa, Dr. Douglas Wilson, Dr. Crystal De Freitas
Dr. Martin Gilboa, Dr. Patricia Juarez, Dr. George Madany,
Dr. Seven Brody, Dr. Ingrid Martinez-Andree, Dr. Irene Chang
Dr. Stephanie Powell, Dr. Adam Breslow, Dr. Patricia Pisinger
Dr. Isabel Baratta, Dr. Sheila Cason, Dr. Thomas Neglia
Dr. Stephen Balch, Dr. Randall Metsch, Dr. David Schmottlach
Dr. Sonja Brion, Dr. Anna Mendenhall, Dr. Nancy Clementino
Dr. Marshall Littman, Dr. Leslie McCormick, Dr. Sharon Sternfeld
Dr. Cara Cohen, Dr. Nicholas Tsoulos, Dr. Elena Fishman
Dr. Hilary Bowers, Dr. Albert Martinez, Dr. Genevieve Minka
Dr. Wendy Chacon, Dr. Leon Kelley, Dr. Victor Lipps, Dr. Jeffrey Selzer, Dr. Lynn Herring, Dr. Teresa O’dea, Dr. Richard Walls, Dr. Vivian Tung, Dr. Christian Archambault, Dr. Veronique James, Dr. Stuart Cohen, Dr. Nancy Shiau, Dr. Linda Smith, Dr. Tori Hardman, Dr. Cheryl Morrell, Dr. Ilene of Zayas, Dr. Bubye, Dr. Andrea Siano, Dr. Aida Martinez, Dr. James Moseman, Dr. Nicholas Levy, Dr. Julie Jones, Dr. Thomas Levy, Dr. Julie Snyder Block, Dr. Lori Warner, Dr. Sheetal Gajwani, Dr. James Jorgensen, Dr. Richard Siegel, Dr. Lori Gould, Dr. Marta Awdykovych, Dr. Janna Cataldo, Dr. Nicole Gorton, Dr. Dania Lindenberg, Dr. Stuart Rubenstein, Dr. Peggy Manuel, Dr. Veda Wu, Dr. Michael Berent, Dr. Gargi Kubal, Dr. Norman Gollub, Dr. Theresa Hardisty, Dr. Jeanne Montal, Dr. Katrina Durkee, Dr. Kamei Tolba, Dr. Carol Hart, Dr. Dennis Butler, Dr. Howard Mehl, Dr. Marta Awdykovych, Dr. Uma Narayan, Dr. Richard McNeal, Dr. Marta Awdykovych Dr. Richard McNeal, Dr. Jennie Ou, Dr. Howard Smart, Dr. Neethi Ratnesar, Dr. Fujii, Dr. Mattson, Dr. Norman, Dr. Sauer, Dr. Gabriela Mogrovejo, Dr. Julie Keeler, Dr. Liz Hourihan, Dr. Dania Lindenberg, Dr. Dori Mortimer, Dr. Marvin Zaguly

To Date

> 30,000 babies screened!
New Behavioral Marker of Autism: Patterns of Eye Gaze
Preference for Social vs. Non-Social Stimuli: Typical 14 MONTHS
New Behavioral Marker of Autism: Patterns of Eye Gaze

Preference for Social vs. Non-Social Stimuli: AT-RISK ASD 15 MO
Abnormal Brain Overgrowth in Autism by 2 to 4 Years of Age

Courchesne et al., 2001

Recent MRI Studies Also Showing Abnormal Brain Overgrowth in Autism by 2 to 4 Years of Age

Sparks et al., 2002
Carper et al 2002
Carper & Courchesne 2005
Hazlett et al., 2005
Schumann, Courchesne 2010
Hazlett et al., 2011
Gray Matter Overgrowth in ASD

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carper et al. 2002</td>
<td>3.4 years</td>
</tr>
<tr>
<td>Bloss &amp; Courchesne, 2007</td>
<td>3.8 years</td>
</tr>
<tr>
<td>Kates et al. 2004</td>
<td>7.6 years</td>
</tr>
<tr>
<td>Palmen et al. 2005</td>
<td>11.1 years</td>
</tr>
<tr>
<td>Hazlett et al. 2005 (left cerebrum only)</td>
<td>19.1 years</td>
</tr>
</tbody>
</table>

* p<0.05
Gray Matter Overgrowth in ASD

1. Carper et al. 2002 3.4 years
2. Bloss & Courchesne, 2007 3.8 years
3. Kates et al. 2004 7.6 years
4. Palmen et al. 2005 11.1 years
5. Hazlett et al. 2005 19.1 years
   (left cerebrum only)
6. Schumann, Pierce et al. 2010 2 years

* p<0.05
Three Phases of Growth Pathology in ASD

Overgrowth

Arrested Growth

Possible Decline/Degeneration

Frontal

Temporal

Amygdala

Courchesne et al 2001

Courchesne et al., 2003

Courchesne & Pierce 2005

Courchesne et al., 2007
RED FLAGS of Autism Spectrum Disorder by 12-24 Months

**Reduced social interest and affect**
- lack of warm, joyful emotional expressions
- lack of sharing emotional enjoyment or interest
- lack of response to name
- lack of showing and interacting

**Abnormal language development**

**Lack of coordination of gaze, facial expression, gesture & sound during interactions**
Abnormal Laterality to Language in ASD Infants & Toddlers

Eyler, Pierce and Courchesne, *Brain*

Temporal cortex

ASD 14 to 47 months

Typical 13 to 45 months

Effect Size (Eta^2)

-0.04 -0.03 -0.02 -0.01 0.00 0.01 0.02 0.03

Left - Right Difference in Mean Amplitude of Response

Age in Months

Typical L > R

ASD R > L
Why Do Some Infants with ASD Get Better?

Are There Biomarkers of Prognosis?
Reduced Functional Connectivity Involved in Social Impairment ASD Infants & Toddlers

Reduced Left-Right Functional Connectivity in ASD Brain

Lower Connectivity Score Correlated with Greater Social Impairment Score

Diagnostic Accuracy is 84% Of ASD Toddlers

Dinstein, Pierce et al 2011
Overgrowth

Autistic (n=7) vs Control (n=6)
Males
Ages 2 to 16 years

Courchesne, Mouton, Calhoun, Arhens-Barbeau, et al 2011, JAMA

79% more neurons in ASD

29% more neurons in ASD
In Normal Development: Neurogenesis in 2\textsuperscript{nd} Trimester Followed by Apoptosis in 3\textsuperscript{rd} Trimester
Overabundance of Neurons in ASD: Possibly Due to Excess Neurogenesis and/or Failure of Apoptosis
2nd TRIMESTER GENESIS OF NEURONS IN HUMANS

Figure 4 from Kreigstein and colleagues Nature 2010 Hansen et al

GW13  GW14  GW15  GW17
3rd trimester apoptosis in humans

Kostovic & Judas 2010
What is the Cause of Excess Cells?

What are the Resulting Cortical Defects?

Gene Expression and CNV analyses

Anatomic Microstructure

79% more DL-PFC neurons
Abnormal Frontal Cortex Gene Expression at Young Ages (2 to 14 years) in Autism

102 differentially expressed genes

Dysregulation of Pathways Governing Cell Numbers and Functional Integrity

- Neurogenesis
- Cell cycle regulation
- DNA damage responses
- Apoptosis and survival
- Cell differentiation
- Immune/Neuroinflammation

Abnormal Down-Regulation of Several Cortical Patterning Genes

- FGF1, HOXD1, NDE1, NODAL, PCSK6

Chow, Pramparo et al., PLoS Genetics, March 2012
Enrichment Analyses of CNVs in DNA from the Same Dorsolateral Prefrontal Tissue Blocks

Chow, Pramparo et al., PLoS Genetics, March 2012
Recurrent Gene Mutations in Small Subset of ASD And Head Circumference

O’Roark, Eichler and colleagues, Science 2012
Abnormal Frontal Cortex Gene Expression at Young Ages (2 to 14 years) in Autism

102 differentially expressed genes

Dysregulation of Pathways Governing Cell Numbers and Functional Integrity

- Neurogenesis
- Cell cycle regulation
- DNA damage responses
- Apoptosis and survival

Cell differentiation

Immune

Abnormal Down-Regulation of Several Cortical Patterning Genes

- FGF1, HOXD1, NDE1, NODAL, PCSK6

Chow, Pramparo et al., PLoS Genetics, March 2012
Examples of near distance microglia-neuron interaction in subjects with autism. A. Process encirclement of a neighboring neuron in the young subject with autism (BTB-4029) that demonstrated the most markedly increased spatial clustering relative to randomness. B. Processes encircling a neighboring neuron in an adolescent subject with autism (UMB-4899) that demonstrated markedly increased local clustering relative to randomness. C. Processes encircling a neuron at a substantial distance from the microglial soma in UMB-4899.
Abnormal Frontal Cortex Gene Expression at Young Ages (2 to 14 years) in Autism

102 differentially expressed genes

Dysregulation of Pathways Governing Cell Numbers and Functional Integrity

- Neurogenesis
- Cell cycle regulation
- DNA damage responses
- Apoptosis and survival

Cell differentiation

Immune

Abnormal Down-Regulation of Several Cortical Patterning Genes

FGF1, HOXD1, NDE1, NODAL, PCSK6

Chow, Pramparo et al., PLoS Genetics, March 2012