Recognition and Intervention of Autism Spectrum Disorder in Children with Dravet Syndrome

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How to identify Autism Spectrum Disorder (ASD)

Relationship of ASD to Epilepsy Syndromes (Dravet)

Management and Treatment of ASD/Social Cognition in Epilepsy
Google, Facebook, Facetime and the Developing Brain

IQ        SQ        Intervention        Outcome
Cognition as part of the Epilepsy phenotype

Cognitive impairments, learning problems, attention and behavioral problems are present at the start of the first seizure or antedate the first seizure in nearly 50% of all children with epilepsy.

In children with epilepsy, cognitive impairments and decline, reflect the severity and dynamics of underlying brain pathology or degree that the distributed neuronal network is affected by the underlying etiology.

Helmstaedter, C., et al. (2014). "Disentangling the relationship between epilepsy and its behavioral comorbidities - the need for prospective studies in new-onset epilepsies." Epilepsy Behav
In a meta-analysis of 24 reports on autism and epilepsy published from 1963 to 2006: Pooled prevalence of epilepsy

- 21.4% in 1485 individuals with autism and intellectual disability (IQ < 70)*

- 8% in 627 persons with autism without intellectual disability (IQ >70)

*The highest rate of epilepsy (46%) occurred in the group with an IQ <40

Amiet, C. et al., Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. Biol Psychiatry 2008

Cross-sectional study using four samples of ASD children Total n=5,815

average prevalence of epilepsy was 12% and reached 26% by adolescence

multivariate regression model: only age and cognitive ability were independently associated with epilepsy

Children age 10 or older had 2.35 times the odds of being diagnosed with epilepsy (p=.001) and for a one standard deviation increase in IQ, the odds of having epilepsy decreased by 47% (p=.001)

Poor language and developmental regression not associated with epilepsy once IQ controlled for
Epilepsy and ASD conceptualized as disorders of large scale neural networks with alterations in cortical-subcortical connectivity

Alterations in minicolumns and selective sparsity of GABAergic interneurons

Abnormalities in neurogenesis and neuronal migration: cellular disorganization, heterotopias and dysplasias

Social and Non-Social Cognition and Epilepsy Share Overlapping Circuitry

STG: superior temporal gyrus  FFA: fusiform face area  IFG: inferior frontal gyrus
IPL: inferior parietal lobe  ACC: anterior cingulate cortex  mPFC: medial prefrontal cortex

Green, M. F., et al. (2015). "Social cognition in schizophrenia." Nat Rev Neurosci
ASD-Epilepsy Shared Mechanism Model

- Intellectual Disability
  - Epileptogenesis
    - Altered neuronal networks/increased I/E ratio
    - Altered structural and molecular connectivity
  - Sociogenesis
  - Shared Mechanisms
- Autisms

Epilepsies
How to identify Autism Spectrum Disorder (ASD)
A) Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays

B) Restricted, repetitive patterns of behavior, interests, or activities

C) Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life)

D) Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
DSM-5 criteria for autism spectrum disorders
An individual must meet criteria A, B, C and D:

A. **Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:**

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

2) **Deficits in nonverbal communicative behaviors used for social interaction**

3) **Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers)**
B) Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following:

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

Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change

Highly restricted, fixated interests that are abnormal in intensity or focus

Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment
C) Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life)

D) Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

*These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur
When Social Skills Are a Warning: Behavior Changes Serve as an Early Signal of Mental-Health Issues; Starting Treatment Sooner

SHIRLEY S. WANG   WSJ

Inferring other peoples thoughts

Social cue perception

Experience sharing

Managing emotional reactions to others

When Social Skills Are a Warning: Behavior Changes Serve as an Early Signal of Mental-Health Issues; Starting Treatment Sooner

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“Social cognition: broadly includes processes used to perceive, encode, store, retrieve, and regulate information about other people and ourselves.”*

Affective Reciprocity: 0 to 6 months

Joint Attention: 6 to 24 months

Theory of Mind: 30 to 36 months

Semantic-Pragmatic Language Disorder/Social Communication Disorder

Cognitive flexibility

*Green, M. F., et al. (2015). "Social cognition in schizophrenia." Nat Rev Neurosci
Diagnosing ASD: Behaviorally Defined Neurological Disorder

Parental concern:

15 to 18 months

Chief Complaint:

Delay in language

Age of diagnosis

3 to 5 years
<table>
<thead>
<tr>
<th>Measure</th>
<th>Function</th>
<th>Administration</th>
<th>Time</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADI-R</td>
<td>Diagnosis</td>
<td>Parent interview</td>
<td>1.5-2.5 hrs</td>
<td>Can differentiate autism from developmental disorders in children with MA as low as 18 months/IQ equivalent=35</td>
</tr>
<tr>
<td>ADOS</td>
<td>Diagnosis</td>
<td>Direct assessment</td>
<td>30-45 mins</td>
<td>Broad developmental coverage. Modules intended for nonverbal children. Toddler version recently developed and available.</td>
</tr>
<tr>
<td>PDD-MRS</td>
<td>Diagnosis</td>
<td>Clinician completed</td>
<td>10-20 mins</td>
<td>Wide age range (2-55). Specifically intended to id autism/ASD in individuals with ID. 12-items completed based on observation/report of behavior over previous 2-6 months.</td>
</tr>
<tr>
<td>M-CHAT</td>
<td>Screener</td>
<td>Parent Interview</td>
<td>Brief</td>
<td>16-30 month age group</td>
</tr>
<tr>
<td>SCQ/SRS</td>
<td>ASD Screener</td>
<td>Parent report</td>
<td>15 mins</td>
<td>Used in age &gt; 4 years with a mental age &gt; 2 years</td>
</tr>
<tr>
<td>VABS-II</td>
<td>Adaptive Level</td>
<td>Parent interview</td>
<td>30-45 mins</td>
<td>Estimate of adaptive functioning and more broadly an index of developmental level</td>
</tr>
<tr>
<td>MSEL</td>
<td>IQ/Developmental Level</td>
<td>Direct assessment</td>
<td>30-45 mins</td>
<td>Widely used in studies of young children with ASD. Provides a composite score as well as standard scores for verbal and nonverbal abilities.</td>
</tr>
<tr>
<td>ABC</td>
<td>Problem behaviors</td>
<td>Parent report</td>
<td>15 mins</td>
<td>Standard tool in AGP and Simons. May provide useful phenotype information</td>
</tr>
<tr>
<td>RBS-R</td>
<td>Repetitive behaviors</td>
<td>Parent report</td>
<td>15 mins</td>
<td>Detailed report of repetitive behaviors and interests common to ASD. Widely used</td>
</tr>
</tbody>
</table>

Table courtesy of Michael Cuccaro
Modified Checklist for Autism in Toddlers (M-CHAT)

The M-CHAT is validated for screening toddlers between 16 and 30 months of age, to assess risk for autism spectrum disorders (ASD). The AAP has endorsed its use at 18 and 24 months of age to screen for autism spectrum disorders.

The questions can be scored in less than 2 minutes using instructions found on http://www.mchatscreen.com.

A trained professional can discuss the responses and guide you to find the right resource. These 23 questions should be accompanied by a follow-up interview which will clarify some of the responses.

Please fill out the following about how your child usually is. Please try to answer every question. If the behavior is rare (e.g., you've seen it once or twice), please answer as if the child does not do it.

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

How to score the M-CHAT. Please score 1 point if you answered “no” to questions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 21 or 22. If your total score was 3 or higher, your child needs a Follow-up Interview with your provider or a health care professional.

Even if you answered “no” to just two or more of questions 2, 7, 9, 13, 14, 15 you should also ask your health care provider to administer the follow-up interview. These are considered critical items of the M-CHAT. Even if your scores are below 3 for the total score and below 2 for the critical questions, and you still have concerns, bring this completed form and your questions to your provider for a more in-depth evaluation or referral.

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www.AutismSpeaks.org
In Recognizing ASD in Epilepsy the Goal is to:

Recognize Atypical Social Cognitive Development Trajectories
Before it is ASD

Determine who is At Risk for Poor Outcome

Intervene Early Before it is ASD
Relationship of ASD to Epilepsy Syndromes (Dravet)
How often do Autism Spectrum Disorders occur in Epilepsy?

32% of 97 children with epilepsy screened positive for ASD
(2005) Epilepsia

15% of 519 patients with epilepsy had ASD
(2010) Brain Dev

37% of 65 children, average age 2.5 years, screened positive for ASD
(2012) Epilepsy Behav

20% of children with new onset and established epilepsies with actionable findings
(2014) Dev Med Child Neurol

21% of 85 children with active epilepsy had ASD
(2014) Pediatrics
Autism Spectrum Disorders in Epilepsy

Nationally representative population-based study (n=7,403)

ASD in population of individuals with epilepsy 16 years and older was 8.1%.

After adjusting for verbal IQ, an individual with epilepsy had a sevenfold increase in the odds of having an autism spectrum disorder.

N= 47 children without ASD and with a normal IQ who were in mainstream

20 children with generalized epilepsy: mean age of 11 years and 6 months (SD 2 years and 6 months)

27 children with focal epilepsy: mean age 11 years and 2 months (SD 2 years and 2 months)

Children with epilepsy had impaired social cognitive skills with deficient pragmatic skills compared to their peers without epilepsy

DSM-5 classification system: Social Communication Disorder
Autism Spectrum Disorder (ASD) in Epilepsy
Prospective Community Based Study (n=555)
(Connecticut Epilepsy Cohort)

5% met criteria for ASD
10% of those whose seizures start in the first 2 years met criteria for ASD
13.8% in those with IQ less than 80 met criteria for ASD
2.2% with normal cognitive abilities met criteria for ASD

West syndrome: 30% with ASD, intellectual impairment, male sex independently associated with ASD

Younger age (of seizures) at onset did not contribute independently to ASD

First Epilepsy than Autism Spectrum Disorder (ASD) (Epilepsy in first year of life)

7% of 84 children with seizures in the first year of life diagnosed with ASD all with intellectual disability

35% (n=6) of 17 children with Infantile Spasms* diagnosed with ASD

*5 other etiologies (symptomatic) and 4 with severe intellectual disability


How often do Autism Spectrum Disorders occur in Dravet?


9 of 37 (24.3%) met criteria for ASD


attention deficit, an inability to inhibit impulsive responses, perseverative responses and deficit in planning function; socialization higher than communication


8 of 13 (65%) patients with ASD


18 of 30 (60%) diagnosed with ASD
1. Autism spectrum disorders and social-cognitive deficits are associated with epilepsy throughout the life-span, and identification of these deficits is an important part of epilepsy care.

2. Children with an epileptic encephalopathy such as infantile spasms are at high risk for developing ASD, and the social-cognitive deficits that precede ASD may be recognized in the first year of life.

3. In epilepsy, the likelihood of developing autism spectrum disorders is highest in those with ID, but there is a wide spectrum of manifestations, from ASD in children with epilepsy and ID, to social-cognitive impairments affecting social interaction and comprehension in those with normal nonsocial cognitive function.

4. Implementation of behavioral, communication, and educational interventions that exist to treat ASD and social-cognitive deficits, along with medications to treat the seizures, should be considered an important part of the comprehensive management of epilepsy throughout the life-span.
Management and Treatment of ASD in Epilepsy

Lesca, G., et al. (2012). "Epileptic encephalopathies of the Landau-Kleffner and continuous spike and waves during slow-wave sleep types: genomic dissection makes the link with autism." *Epilepsia*

Bitton, J. Y., et al. (2015). "Does treatment have an impact on incidence and risk factors for autism spectrum disorders in children with infantile spasms?" *Epilepsia*
Do we need to treat the etiology that leads to Epilepsy and ASD?


Can we treat the process that leads to Epilepsy and ASD?

Nabbout, R., et al. (2013). Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. Orphanet J Rare Dis
Treating the seizures is necessary BUT to improve developmental outcomes not sufficient
<table>
<thead>
<tr>
<th>Medication</th>
<th>Target behaviour</th>
<th>Evidence</th>
<th>On- or off-label</th>
<th>Adverse events*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical antipsychotic medications (i.e., aripiprazole risperidone)</td>
<td>Irritability, aggression†</td>
<td>Multiple, well-designed RTCs supporting their use⁶⁹,⁷⁵</td>
<td>FDA indication</td>
<td>Weight gain, metabolic syndrome, gastrointestinal effects, sedation, akathisia, orthostatic hypotension, tachycardia, extrapyramidal syndrome, neuroleptic malignant syndrome (rare)</td>
</tr>
<tr>
<td></td>
<td>Repetitive behaviours‡</td>
<td>≥ 2 large RCTs support efficacy (although not a primary outcome measure)⁶⁹,⁷⁵</td>
<td>Off-label</td>
<td></td>
</tr>
<tr>
<td>Serotonin reuptake inhibitors</td>
<td>Repetitive behaviour§</td>
<td>1 unpublished and 1 published large RCT (fluoxetine, citalopram): no evidence for efficacy⁷⁰</td>
<td>Off-label, unless comorbid obsessive–compulsive disorder</td>
<td>Gastrointestinal effects, insomnia, agitation, disinhibition, dry mouth, headache, sexual dysfunction</td>
</tr>
<tr>
<td></td>
<td>Anxiety or depression</td>
<td>None in autism, but multiple studies for pediatric anxiety disorders and depression</td>
<td>On-label for anxiety disorders and depression</td>
<td></td>
</tr>
<tr>
<td>Stimulants</td>
<td>ADHD-like symptoms¶</td>
<td>&gt; 2 RCTs (methylphenidate) support its use⁷⁶; smaller studies support longer-acting stimulants</td>
<td>On-label for ADHD</td>
<td>Poor appetite, weight loss, irritability, insomnia</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>ADHD-like symptoms**</td>
<td>1 large, 1 small RCT support effectiveness⁷⁷,⁷⁸</td>
<td>On-label for ADHD</td>
<td>Gastrointestinal effects, insomnia, orthostatic hypotension</td>
</tr>
<tr>
<td>α-agonists</td>
<td>ADHD-like symptoms</td>
<td>Several small RCT and open label studies in autism support efficacy⁷⁹</td>
<td>Clonidine: off-label; guanfacine: FDA indication for ADHD††</td>
<td>Somnolence, hypotension, bradycardia, dry mouth, constipation, irritability</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Initial insomnia‡‡</td>
<td>Cochrane meta-analysis, positive effect on initial insomnia compared to placebo⁸⁰</td>
<td>Not regulated</td>
<td>Headache, dizziness and nausea (all rare outcomes)</td>
</tr>
</tbody>
</table>
Pharmacological treatment of the behaviors that define ASD (social cognitive function) may be necessary but to improve developmental outcomes not sufficient.
Can developmental based behavioral early intervention improve developmental outcomes in epilepsy syndromes?

Early Intensive Behavioral Intervention (EIBI)

- Highly structured teaching approach
- Well-established treatments for ASD
- Rooted in principles of applied behavior analysis (ABA)

“applied behavior analysis (ABA),” the science of understanding how changes in the environment affect human behavior
The core elements of EIBI:

Specific teaching procedure referred to as discrete trial training

Use of a 1:1 adult-to-child ratio in the early stages of the treatment

Implementation in either home or school settings

Range of 20 to 40 hours per week across one to four years
implemented in natural settings

involve shared control between child and therapist

utilize natural contingencies

use a variety of behavioral strategies to teach developmentally appropriate and prerequisite skills

J Autism Dev Disord Published Online March 4 2015

Randomized, Controlled Trial of an Intervention for Toddlers With Autism: The Early Start Denver Model: Dawson, Rogers, et al, 2010; Pediatrics

18 to 30 month old with autism spectrum disorders (n=48) Randomized into two groups and followed for 24 months:

**ESDM group:** 20 hour per week behavioral-developmental intervention, plus parent training, plus community intervention

**Assessed and Monitored:** included about 10 hours of community intervention
Randomized, Controlled Trial of an Intervention for Toddlers With Autism: The Early Start Denver Model: Dawson, Rogers, et al, 2010; Pediatrics

**Outcome in ESDM group:**

- Improved cognitive (IQ raised by 17 points mostly language)
- Adaptive skills improved but not RRBI
- Diagnostic status changed to more mild group
A follow up study using the Early Start Denver Model in toddlers with ASD:

found that after 2 years of treatment, toddlers receiving the treatment (ESDM group) demonstrated an EEG pattern (based on an alpha: theta ratio) similar to that of typically developing children

**increased cortical activation (decreased alpha power and increased theta power) when viewing faces**

This EEG pattern related to gains in social behavior

Current available pharmacological and EIBI treatments of the behaviors that define ASD (social cognitive function) and pharmacological treatments of seizures may be necessary BUT to improve developmental outcomes not sufficient


<table>
<thead>
<tr>
<th>Genetic variant or syndrome</th>
<th>Relevant genes</th>
<th>Epilepsy features</th>
<th>Developmental features</th>
<th>Potential treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2p16.3 deletion</td>
<td>NRXN1</td>
<td>Early onset, generalized, severe</td>
<td>Profound ID, ADHD</td>
<td></td>
</tr>
<tr>
<td>7q35 deletion (cortical dysplasia-focal epilepsy)</td>
<td>CNTNAP2</td>
<td>Both focal and generalized epilepsy</td>
<td>Profound ID, Profound language impairment</td>
<td>Oxytocin</td>
</tr>
<tr>
<td>15q11.2-13.1 duplication</td>
<td>UBE3A, GABA&lt;sub&gt;a&lt;/sub&gt; receptors</td>
<td>Varied: Generalized and partial, multi-focal, infantile spasms, possibly resistant to typical benzodiazepenes</td>
<td>Hypotonia, Comorbid ID and ASD, Profound language impairment, Excessive beta band activity</td>
<td>Benzodiazepenes may be less effective</td>
</tr>
<tr>
<td>18q12.1 duplication or deletion</td>
<td>DTNA Cadherin superfamily genes</td>
<td>Focal and generalized</td>
<td>ID, language delay, deletions associated with motor delay</td>
<td></td>
</tr>
<tr>
<td>22q13.3 deletion</td>
<td>SHANK3</td>
<td>Varied: generalized, focal, absence</td>
<td>Hypotonia, Comorbid ID and ASD, Profound language impairment</td>
<td>IGF-1</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>FMR1</td>
<td>Focal epilepsy, often with centrotetemoral spikes</td>
<td>Comorbid ID, with ASD severity related to IQ, anxiety, sleep impairment</td>
<td>MGLuR5 antagonists, NMDA antagonists (Memantine), GABA modulators (riluzole, acamprosate)</td>
</tr>
<tr>
<td>MECP2-related disorders (Rett syndrome)</td>
<td>MECP2</td>
<td>Generalized and multifocal, EEG shows background slowing (delta power), loss of normal sleep architecture</td>
<td>Microcephaly, regression, Profound ID, stereotypic hand movements, gait dyspraxia, hypotonia</td>
<td>IGF-1, Valproate</td>
</tr>
<tr>
<td>PTEN related disorders</td>
<td>PTEN</td>
<td>Both focal and generalized</td>
<td>Macrocephaly, comorbid ID</td>
<td>mTORc inhibitors</td>
</tr>
<tr>
<td>Tuberous Sclerosis Complex</td>
<td>TSC 1/2</td>
<td>Infantile Spasms, Generalized and multifocal epilepsy</td>
<td>Comorbid ID, non-verbal IQ decline in early infancy, anxiety and ADHD</td>
<td>mTORc inhibitors, Vigabatin</td>
</tr>
</tbody>
</table>

Moving Forward: Comprehensive Treatment Approach to ASD in Epilepsy

Treatment protocols in Epilepsy-ASD that modify-enhance early socio-cognitive developmental trajectories

Early Intensive Behavioral Intervention combined with Mechanistic-based Pharmacotherapies
THANK YOU FOR LISTENING