

## ASD-new knowledge Stockholm March 2010

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### The Early Symptomatic Syndromes Eliciting Neuropsychiatric/Neurodevelopmental Clinical Examinations (ESSENCE)

- **Syndromes**
  - ASC (Autism Spectrum Conditions, including Disorders)
  - ADHD (Attention-Deficit/Hyperactivity Disorder Spectrum) with or without ODD/CD (Oppositional Defiant Disorder/Conduct Disorder)
  - TS (Tic Spectrum including Tourette Syndrome)
  - BD (Bipolar Spectrum including Disorder)
  - SLI/LI ("Specific" Language Impairment)
  - LD/MR (Learning Disability/Mental Retardation), NVLD (Non-Verbal Learning Disability), Working Memory Disorder, and Slow Processing Disorder
  - DCD (Developmental Coordination Disorder)
  - BPS (Behavioural Phenotype Syndromes)
  - Epilepsy Syndromes: Landau-Kleffner Syndrome and CSWS

## The Early Symptomatic Syndromes Eliciting Neuropsychiatric Clinical Examinations (ESSENCE)

- **Major symptoms from one or more (usually several) of the following domains before age 4 years**
  - General development
  - Motor control/Perception-Sensory
  - Communication/Language
  - Activity/Impulsivity
  - Attention
  - Social interaction/Reciprocity
  - Behaviour
  - Mood swings
  - Sleep
  - Feeding

## The Early Symptomatic Syndromes Eliciting Neuropsychiatric/Neurodevelopmental Clinical Examinations (ESSENCE)

- **Example: delayed language at 2.5 years**
  - Screen takes no more than 5 minutes (deviance if comprehension difficulties, fewer than 25 communicative words, major dysarticulation)
  - About 6% of all children screen positive and have “confirmed” language delay at 2.5 years
  - **Screen positive and confirmed language delay at 2.5 years => 70% have “neuropsychiatric/neurodevelopmental” diagnosis (with clinical impairment) at age 7 years (ADHD, ASD, LD, DCD), virtually all have remaining speech-language problems**
  - i.e. all children with “SLI”/LI at 2.5 years need to be followed carefully and vast majority will need services
    - Miniscalco et al 2005, 2006, 2007, 2009

## The Early Symptomatic Syndromes Eliciting Neuropsychiatric/Neurodevelopmental Clinical Examinations (ESSENCE)

- **Example: suspected ASD under age 3 years**
  - 28 children followed for several years from under age 3 years with suspected ASD: 75% met criteria for autistic disorder at age 6 years, and remainder had other neuropsychiatric diagnosis (other ASD, ADHD, LD)
    - Gillberg et al 1990
  - 208 children with ASD diagnosis made by clinicians at age 0-4 years: 52% met criteria for autistic disorder at follow-up, 39% met criteria for other ASD, 9% had other neuropsychiatric diagnosis (ADHD, LD) - prevalence of ASD in this age group 0.6%
    - Fernell et al 2009
  - **ASD diagnosis around age 2-4 years highly stable in 90% of cases, virtually no “over-diagnosis”, many Asperger cases missed**

## Early symptoms (age 0-4 years) in ASD

- **Motor control problems first year of life (Moebius-like face, strange movements from back to front, compartmentalised motor development) 50-100%**
- **Perceptual abnormalities in 90-100%**
- **Language problems/pragmatic problems in 90-100%**
- **Behaviour problems in 90-100%**
- **No or limited initiation of joint attention ( => major social interaction problems) 80-100%**
- **Hyperactivity (often extreme) in 40-50%**
- **Hypoactivity in 10-25%**
- **Sleep problems in 40%**
- **Delayed general development in 20%**
- **Mood swings in 10%**
- **One or several of the above could be presenting complaint**

## Early symptoms (age 0-4 years) in ADHD

- **Motor control problems first year of life 50-100%**
- **Perceptual-sensory abnormalities in 50-100%**
- **Language problems/pragmatic problems in 50%**
- **Behaviour problems in 50-100%**
- **Hyperactivity (sometimes, but rarely, extreme) in 30-50%**
- **Hypoactivity problems and inattention in 25%**
- **Sleep problems in 40%**
- **Delayed general development in 15%**
- **One or several of the above could be presenting complaint**

## Scope of problem: preschool

- **At least 5% of children under 6 years are affected by child neuropsychiatric problems, i.e. ADHD, ASD, tic syndromes (7% of boys, 3% of girls)**
- **At least 6% of children under 3 years are affected by language delay (marked overlap with neuropsychiatric problems)**
- **Another several per cent are affected by various kinds of psychosocial problems**
- **Some children have subclinical indicators that they will develop clinical problems later**
- **Therefore: a public health problem**
- **Indications that for some disorders early intervention may make substantial difference (autism, ADHD, CD)**

## Scope of problem: school and adolescence

- **At least 10% of children under 18 years of age are or have been affected by psychiatric disorders (12% of boys, 8% of girls) - including ADHD, ASD, TS, CD, BD (and psychosis, eating disorder, depression, and anxiety disorders)**
- **Another 10% or more are affected by various kinds of psychosocial problems (including drug abuse), some of which may be triggered by or interacting with ESSENCE**
- **About 5% are affected by “dyslexia” (more than half of whom subsumed in previously mentioned groups)**
- **1-2% are affected by LD**
- **Overlap/”Comorbidity”/Co-existence substantial**
- **When looking back: vast majority had symptoms <5 years**

## ADHD as an example of ESSENCE

- **ADHD occurs in 4-7% of all school age children according to studies performed in Sweden, Denmark, Norway, Finland, Iceland, Germany, Spain, Australia, Brazil, Canada and the US; probably half of these are recognized or can be recognized under age 6 years**
- **Severe variants are at a rate of at least 1.5-3% of the general population or a little under half of all cases meeting diagnostic criteria for the disorder; these are the ones most likely to be recognized in very young children**

## ADHD and underrated comorbidities

- **Any significant comorbidity 85-100%**
- One comorbidity 85-100%
- Two comorbidities 65-70%
- Three comorbidities 35-50%
  - Extreme clinical disability

## Overlap and issues

- Is ODD not a comorbidity but an index of severity in ADHD?
- Are learning problems a result of non-assortative mating in parents?
- Are DCD problems an index of a link with ASD?
- Is ASD a very common comorbidity signalling some shared genes?
- Are ASD and ADHD in some cases on the same spectrum?

## Tourette syndrome and bipolar disorder

- Is early onset extreme “ADHD” = ASD?
- Is early onset ADHD, mainly hyperactive-impulsive subtype with family history of tics = Tourette syndrome?
- Or of Tourette syndrome with ADHD?
- Is early onset ADHD with severe mood swings and a family history of bipolar disorder = early onset bipolar disorder?
- Or of bipolar disorder with ASD?

## ASD

- One per cent or a bit more of the general population of children (Gillberg et al 1991, Gillberg and Wing 1999, Wing and Potter 2002, Baird et al 2006, Gillberg et al 2007 a and b, Baron-Cohen et al 2009)
- Half recognized in children under 6 years of age (Fernell et al 2009)
- Main presenting symptoms: motor-perceptual-sensory, attention, activity, learning, sleep, social, and language

# ASD

- ASD is a dyad, not a triad (the dyad of social communication impairment and extreme repetitive behaviours)
- DSM-V will probably have six symptoms that correspond to eight of the DSM-IV symptoms and four vague criteria have been removed
- In the new manual, only autistic disorder and Gillberg's Asperger syndrome will meet the new criteria, most PDDNOS will "disappear"

## ASD: background factors

- ASD is a group of multifactorially determined conditions, and there are almost as many different causes as there are cases. Genes play a major role, but environmental factors contribute to clinical presentation in many cases and can themselves cause ASD in some instances. The prefrontal, temporal, brainstem and cerebellar regions of the central nervous system are usually affected. These areas constitute a functional network, "the default network", which appears to be critically differently functioning in ASD
  - Iacoboni 2006, Buckner and Vincent 2007, Monk et al 2009, Coleman and Gillberg 2010

## ASD: genetic factors

- **Neurologin, neurexin, SHANK-3 and glutamate genes in ASD**
- **DRD-3 gene affected in ASD (stereotyped behaviours)**
- **DRD-4 and DAT-genes affected in children (and DRD-5) with ADHD**
- **DRD-5 gene affected in adults**
- **Noradrenaline-related genes (NET)**
- **SNAP25 affected in children and adults with ADHD**
- **Melatonin-gene (related to sleep problems?) in ASD and ADHD**
- **Other dopamine-related genes in ASD and ADHD?**
- **Serotonin?**

– Comings et al 2000, Jamain et al 2003, Taylor et al 2007, Kim et al 2007, Bourgeron et al 2008, Melke et al 2008, Gizer et al 2009, Bourgeron, Gillberg et al 2010

## ASD: genetics

- "Mutations in TSC1/TSC2, NF1, or PTEN activate the mTOR/PI3K pathway and lead to syndromic ASD with tuberous sclerosis, neurofibromatosis, or macrocephaly. Mutations in NLGN3/4, SHANK3, or NRXN1 alter synaptic function and lead to mental retardation, typical autism, or Asperger syndrome. The mTOR/PI3K pathway is associated with abnormal cellular/synaptic growth rate, whereas the NRXN-NLGN-SHANK pathway is associated with synaptogenesis and imbalance between excitatory and inhibitory currents. Taken together, these data strongly suggest that abnormal synaptic homeostasis represent a risk factor to ASD."
- Bourgeron 2008

## ASD: genetics

- Synapse and clock genes interact in the “protection against” autism and ADHD. Variant/mutant synapse/synapse scaffolding genes lead to impaired neural networks that underpin ASD symptomatology (and ADHD?). Variant/mutant clock genes (melatonin) disrupt sleep and circadian/seasonal rhythms and affect ASD and ADHD symptomatology
  - Toro, Gillberg, Leboyer, Bourgeron 2010

## ASD: genetics

- ”The key to understanding the genetics of ADHD is to accept very considerable heterogeneity with different genes having effects in different families and in different individuals. It is too early to interpret the new wave of genome-wide association and copy number variant studies but preliminary data support the overlap with affective disorder genes and also with CNS connectivity genes likely to be involved in autism and affective disorders.”
  - Sharp et al 2009

## Mental retardation/Learning disability

- Two per cent of the general population of children
- Half recognized in children under 6 years of age
- Main presenting symptoms: motor-perceptual, attention, activity, general learning, and language
- 15-60% have ASD!
- LD very often missed!
- Most taboo of all diagnoses!
- Borderline intellectual functioning “behind” a lot of “neuropsychiatric diagnoses”

## Behavioural phenotype syndromes

- 0.6-0.9% of general population of children
- All potentially recognizable before age 6 years
- 80% have LD (22q11 and FRAX often not LD)
- Main presenting symptoms: general development delayed, motor-perceptual-sensory, feeding, physical, stigmata, attention, activity, social, “ASD”, learning, and language

## ADHD: implications

- ADHD is always a signal that comorbidities **SHOULD BE SCREENED** for
- Most of the comorbidities (except ODD and DCD) are probably unresponsive to stimulants
- Some of the comorbidities respond to physiotherapy (DCD), CBT (OCD, anxiety), psychoeducation (autism, academic failure) or other medications (depression, tics, OCD)

## ADHD: some issues

- The fact that “ADHD” is almost always comorbid with other **MAJOR** disorders begs the question
- Is ADHD a biologically valid “reaction” to a whole host of other brain problems?
- Or is ADHD the “underlying” problem in a lot of differently diagnosed disorders?
- ADHD in women missed and misdiagnosed (GAD, memory problems, depression) - estrogen has protective effects
- In any case: the comorbidities of ADHD need to be studied in much more detail

## ASD: implications

- ASD is always a signal that comorbidities **MUST BE SCREENED** for
- ADHD in ASD is often responsive to treatment
- Psychoeducation and behaviour therapy first and foremost

## ASD: some issues

- Severe cases should all be recognized in preschool (majority under 3 years of age)
- Asperger syndrome will not usually be diagnosed until school age
- Severe hyperactivity/"ADHD" often major presenting symptom

## Tourette syndrome diagnosis and intervention

- Almost never handicapping in preschool age  
UNLESS there is comorbid ADHD
- Severe cases of Tourette syndrome comorbid with ADHD, OCD, and ASD in vast majority of cases
- Tics should not be treated with medication unless extreme

## Gender issues

- Boys much over-represented generally among preschool children with mental health problems
- But many girls are currently missed and diagnosed only in adolescence and adult age
- Women remain misdiagnosed throughout life in the vast majority of cases (true of ASD and ADHD and other ESSENCE)

## ASD-ESSENCE conclusions

- ASD, ADHD, TS, bipolar disorder, LD, SLI, DCD etc. overlap to a marked degree throughout life and are often not clearly separable under age 5 years
- All children presenting with major and impairing ESSENCE symptoms (developmental delay, language delay, motor control problems, perceptual-sensory problems, activity problems, inattention, social interaction, general behaviour, mood or sleep problems) need to be followed up
- Even though refined diagnosis is needed in all cases, at early stages ESSENCE may be the only “safe” label
- Never proclaim: “He/she will grow out of it” - no evidence whatsoever that this is likely to happen in more than a small minority of cases

## ASD-ESSENCE conclusions

- ASD should be evaluated and diagnosed in centres that have full capacity for all of ESSENCE
- ASD needs intervention by specialists
- ASD should be followed up at the ESSENCE centre
- ASD-ESSENCE needs full medical work-up in all cases, current situation is terrible worldwide, still seen as an educational-psychological (and not medical) problem
- Consider ASD-ESSENCE in everyone presenting with a problem!