Autism spectrum disorders: are we there yet?

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Autism spectrum disorders

- Diagnostic concepts and clinical presentations
- Prevalence/incidence/epidemiology
- Acquired brain lesions and ”comorbidity”
- Genetics
- Where in the brain is autism?
- Psychosocial interactions
- Intervention
- Outcome
- The future

Diagnostic concepts and clinical presentations

- At least four clinical presentations of autism (autism/autistic spectrum disorder) plus ”one” non-clinical
- 1. Autistic disorder (Kanner syndrome) which can be subdivided into ”low-functioning” (”Wing´s triad with severe learning disability/MR”) and ”relatively high-functioning”
- 2. Asperger’s disorder (Asperger syndrome)
- 3. Childhood disintegrative disorder (Heller syndrome) - different from ”late onset autism”?
- 4. PDD NOS (atypical autism, other autistic-like condition, other autism spectrum disorder)
- (5. The broader autism phenotype (lesser variant, shadow syndrome, autistic featutres) - part of spectrum?)

Prevalence, incidence/epidemiology

- **Prevalence** much higher than believed in the past: ASD in 1% of population, AD in 0.2%; many studies of prevalence, very few of **incidence; no good evidence that overall rates have soared, but subgroup variation likely; ASD was always quite common? - 0.7% already in the 1970s in Sweden**
- Associated with **mental retardation** 15% (80% in autistic disorder/AD)
- Associated with **epilepsy** 5-10% (35% in AD)
- **Medical disorder** in 10% (25% in AD)
- Skewed **male:female ratio** 2-4:1
- High rate of **visual, hearing and motor impairments (including at birth)**
- **Sibling rate raised; identical twin rate much raised** in classic autism
  - **Rutter 1971, Wing 1981, Gillberg 1983, Gillberg & Coleman 1996, Gillberg 1999, Fombonne 2003**

”Acquired” brain lesions and co-existing disorders (”medical co-morbidity”)

- Tuberous sclerosis, Fragile X syndrome, Partial tetrasomy 15, Down syndrome, XYY, XO, Hypomelanosis of Ito, Rett complex variants, Angelman syndrome, Williams syndrome, CHARGE association, Smith-Magenis syndrome, Smith-Lemli-Opitz syndrome, CATCH 22, Fetal alcohol syndrome, Retinopathy of prematurity, Thalidomide embryopathy, Valproic syndrome, Moebius syndrome, Silver-Russell syndrome, (Landau-Kleffner syndrome), Herpes and rubella infection
  - Gillberg & Coleman 2003

Acquired brain lesions/ medical co-morbidity

- **Known medical disorders** 25% in autistic disorder ”proper” (unselected samples) and 2-10% in Asperger syndrome
- These are either **genetic** in their own right, affect autism susceptibility gene areas, or cause brain lesions through direct/indirect insults
- High rate of **pre- and perinatal risk factors**
  - Gillberg & Coleman 2000

Acquired brain lesions/ medical co-morbidity

- **Tuberous sclerosis**
  - 3-9% of all autism cases, more common in those with epilepsy
  - chromosome 16p involved in one variant (autism susceptibility genetic area? ADHD susceptibility genetic area)
  - dopamine genes on chromosome 9 affected in other TS variant
  - autism likely if TS lesions in temporofrontal regions and if there are many lesions
    - Gillberg et al 1996, Bolton et al 1997

Acquired brain lesions/ medical co-morbidity

- **Herpes encephalitis**
  - affects temporofrontal areas more often than other brain structures
  - can lead to classic symptoms of autism even in previously unaffected individuals who are 14 and 31 years of age
    - Gillberg 1986, Gillberg IC 1991, Ghaziuddin et al 2002

Acquired brain lesions/ medical co-morbidity

- **Thalidomide embryopathy**
  - Pattern of eye-abnormalities (including Crocodile-tears) and limb anomalies in those with autim dates the autism to 20-24 days post-conception
  - 5% have classic autism (with or without MR)
    - Strömland et al 1994

Psychiatric ”co-morbidity”

- **ADHD/HKD (often part of autism in early life)**
- **Tics (complex similar to stereotypies)**
- **OCD (part of the triad?)**
- **Anxiety (often strong environmental factors)**
- **Depression**
- **Bipolar disorder**
- **Selective mutism**
- **Most with AS will meet criteria for personaliy disorder (inappropriate to diagnose?)**
- **Eating disorders (including anorexia nervosa)**
- **Sleep disorders**

  – **Gillberg & Billstedt 2000**

Genetics

- **Sibs affected** in 3%: core syndrome
- **Sibs affected** in 10-20%: spectrum disorder
- **Identical co-twins** affected in 60-90%
- **Non-identical co-twins** affected in 0-3%
- All of these findings refer to probands with autism proper, not spectrum disorders
  - Rutter 2002, Gillberg 2002

Genetics

- **First-degree relatives** increased rates of affective disorders (including bipolar), social phobia, obsessive-compulsive phenomena, and ”broader phenotype symptoms”
- **First-degree relatives also show** possibly increased rates of learning disorders including MR, dyslexia and SLI
- What about ADHD? Tics?

Genetics

- Genes on certain chromosomes (e.g. 2, 6, 7, 16, 17, 18, 22, and X) may be important (genome scan studies of sib-pairs)
- Clinical findings in particular syndromes such as partial tetrasomy 15 (15q), Angelman (15q), tuberous sclerosis (9q, 16p), fragile X (X), Rett syndrome (X), Turner syndrome (X)
  - Betancur 2003

Genetics

- **Neuroligin** genes on X-chromosome mutated in some cases
- Neuroligin genes on other chromosomes, including chromosome 17
- **Other neurodevelopmental genes** according to microarray study
  - Jamain, Bourgeron, Leboyer, Gillberg et al 2003, Laumonnier et al 2004, Chi et al 2004, Larsson, et al 2004

Where in the brain is autism?

- **Clinical finding**: macrocephalus common
- **Acquired brain lesions** implicate fronto-temporal and bilateral dysfunction in core syndrome; right or left dysfunction in spectrum disorder
- **Autopsy data** suggest: amygdala, pons and cerebellum
  - Bayley et al 1997, Bauman 1988, Gillberg & Coleman 2000, Gillberg & deSouza 2002

Where in the brain is autism?

- **Brainstem** damage suggested by
  - Thalidomide
  - Moebius syndrome, CHARGE association, and Goldenhar syndrome
  - Auditory brainstem responses
  - Decrease in/lack of postrotatory nystagmus
  - Aberrant muscle tone and concomitant squint
    - Ornitz & Ritvo 1967, Ornitz 1977, Strömland, Gillberg et al 1994, Gillberg & Steffenburg 1997, Gillberg & Coleman 2000, Rosenhall, Gillberg et al 2003, Johansson et al 2004

Where in the brain is autism?

- **Cerebellar** dysfunction suggested by
  - **Autopsy** studies
  - **Imaging** studies
  - Relationship to **ataxia**
    - Courchesne 1988, Bauman et al 1992, Bayley et al 1999, Oldfors, Gillberg et al 2000, Weidenheim, Rapin, Gillberg et al 2001, Åhsgren, Gillberg et al 2004

Where in the brain is autism?

- **Frontotemporal** brain dysfunction suggested by
  - Autopsy studies
  - Functional imaging studies
  - Neuropsychological studies
  - Combined neuropsychological-neuroimaging studies
  - Clinical picture
    - Gillberg 1999, Gillberg 2002

Where in the brain is autism?

- **Neuropsychological studies show**
  - Metarepresentation problems
  - **Aberrant reading of facial expressions**
  - **Aberrant/unusual face processing**
  - Non-verbal learning disability in AS
  - Verbal learning disability in AD
  - Executive function deficits
  - Central coherence problems
  - Procedural (complex) learning deficits
  - Superior fact learning
    - Ozonoff 1994, Happé 1994, Nydén et al 2000, Baron-Cohen et al 2002, 2003, Minshew 2003, Frith 2004, Cederlund & Gillberg 2004

Where in the brain is autism?

- **At least four biological variants of autism?**
  - Early brainstem/cerebellar associated with severe secondary problems (and low-functioning autism with little or no language)
  - Midtrimester bitemporal lobe damage (and classic autism with some-considerable language)
  - Uni- or bilateral frontotemporal dysfunction in high-functioning individuals (with Asperger syndrome with good formal expressive language)
  - Multi-damage autism (autism with severe-profound MR and some atypicality)
    - Gillberg 2003 (Rutter lecture)

Where in the brain is autism?

- Likely that **several functional neural loops are implicated** and that all impinge on neurocognitive/social cognitive functions that are crucially (but possibly not specifically) impaired in autism
  - Gillberg 1999, Gillberg & Coleman 2000

Psychopharmacology of autism

- Dopamine (Gillberg et al 1987)
- Serotonin (in MR also) (Coleman 1976)
- Noradrenaline (Gillberg et al 1987)
- Neuroligins (Jamain et al 2003)
- GFA-protein (Ahlsén et al 1993)
- Gangliosides (Nordin et al 1998)
- Endorphines (Gillberg et al 1985)
- Glycine, GABA, Ach, glutamate?
- Immune system (Plioplys 1989)

Clinical psychopharmacology of autism

- Only dopamine antagonists (old and new neuroleptics) have been shown to affect some core symptoms of autism in young children; however, important side-effects, including atypical weight-gain with risperidone; these agents are particularly helpful for irritable-disruptive and self-injurious behaviours
- SRIs for severe OCS and anxiety
- Stimulants for severe ADHD
- Antiepileptics for epilepsy (and mood swings?)
- Peptides?? And peptide-targeted drugs?
  - Campbell et al 1976, van Buitelaar 2000, McCracken et al 2002, Lindsay & Aman 2003, Martin et al 2004, McDougle 2004

The pathogenetic chain

- **Genetic** or **environmental** insult
- Damage or **neurochemical dysfunction**
- **Neurocognitive and social cognitive functions restricted** (procedural learning, face processing, metarepresentations, central coherence, executive functions)
- **The ”syndrome” (or, sometimes, the ”arbitrary” symptom constellation) of autism**
- **The dyad (not triad) of social/communication impairment plus the monad of restricted behaviour pattern as a frequent concomitant? or three monads with frequent co-existence?**

Psychosocial interactions

- Not associated with social class
- Not associated with psychosocial disadvantage; however, “pseudoautism” described in children exposed to extreme psychosocial deprivation
- Temporally restricted major improvement in good psychoeducational setting
- Immigration links? Indirect link with genetic factors?

Psychosocial interactions

- Abnormal child triggers unusual interactions
- Some parents have autism spectrum disorders themselves - not necessarily a major problem in all cases
- Anxiety, violent behaviours, self-injury and hyperactivity reduced in “autism-friendly” environment

Intervention

- All people are individuals first and foremost; at least as true in autism as in “neurotypicality”
- People WITH autism; not autistic people!
- Change attitudes
- Respect for people in the autism spectrum
- Focus on changing environment and
- Foster adaptive skills

Intervention

- If known underlying disorder: treat this (and be aware of syndrome-specific symptoms such as gaze avoidance in fragile X)
- If epilepsy: treat this (however, there are major caveats here)
- If hearing, vision, or motor impaired: treat this
- If important psychiatric co-existing problems (SIB, ADHD, OCS, bipolar): threat these
- Psychoeducational measures
- ABA
- Symptomatic biological treatments

Intervention

- No medication for many; autism “per se” not an agreed target for medication trials
- Atypical neuroleptics (violence, self-injury, sleep problems, hyperactivity), antiepileptics (seizures, epileptogenic discharge?, bipolar), SSRIs (OCS, depression), stimulants (ADHD), lithium (and other drugs) for some
- Other medications?
- Diets??

Intervention

- Physical exercise!!
- “Sensory awareness” environment (reduce noise, certain sounds, smell etc.)
- Autism-friendly environment
- Concrete, visual (not always), straight-forward
- Minimize ambiguities and symbolic interpretation

Outcome

- Very variable
- Poor in low- and middle-functioning cases with AD
- Better with early diagnosis?
- Language at age 3 = likely later Asperger phenotype?
- No language at age 7 = likely never much spoken language
- Majority probably live to be old, but increased mortality in subgroup (with medical disorders only?)
- Basic problems remain, albeit modified
- High rate of “secondary” psychiatric problems (personality disorder, affective, social, catatonia)

The future

- Specific knowledge (including genetic and neurophysiological) and treatment for subgroup
- New diagnostic criteria
- Symptomatic treatments
- Psychoeducation/ABA
- Acceptance and attitude change!
- People with autism, not autists or autistic people! Cannot be stressed enough
- Respect for people with functional disabilities!

Literature

- Gillberg C & Coleman M (2000) The Biology of the Autistic Syndromes, Third Edition. Cambridge University Press
- Gillberg C (2002) A Guide to Asperger Syndrome. Cambridge University Press
- Plus 300 PubMed scientific papers at ncbi.nlm.nih.gov