

Autism spectrum disorders: recent developments

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Autism spectrum disorders (ASD)

- 4 Clinical features
- 4 Epidemiology
- 4 Chromosomes and genes
- 4 Environmental risks
- 4 Psychosocial factors
- 4 Brain basis
- 4 Outcome
- 4 Medical and other interventions
- 4 The future

Clinical features

- 4 At least four **clinical** variants of **ASD** ("monad", "dyad" or "triad" of social impairment)
- 4 **Autistic disorder**/childhood autism (Kanner syndrome) - one with (20%) and one without regression (80%)
- 4 **Asperger's disorder**/"high-functioning" autism (Asperger syndrome)
- 4 **Childhood disintegrative disorder** (Heller syndrome)
- 4 **PDD NOS/Atypical autism** (other autistic-like condition)
- 4 ("Broader phenotype"; "Autistic features"?)

Clinical features: childhood autism

- 4 Onset before 3 years of age of
- 4 I. Severely restricted development of reciprocal social interaction
- 4 II. Severely restricted development of reciprocal communication affecting both verbal and no-verbal domains
- 4 III. Severely restricted development of imagination and variability of behavioural repertoire

Clinical features: childhood autism (DSM-IV and ICD-10)

- 4 Both DSM-IV and ICD-10 are problematic in that they either rule out or warn against making a diagnosis of other conditions co-existing with autism (e.g. ADHD, bipolar and psychotic disorders)
- 4 Disregard this criterion!

Clinical features:

Asperger syndrome

- 4 **Asperger syndrome** according to ICD-10/DSM-IV (1993, 1994) does not exist or is so rare as to be clinically meaningless (Leekam et al 2000)
- 4 **Gillberg (1988) and Szatmari (1989) criteria** were modelled around Asperger's own descriptions
- 4 **Are all cases of Asperger syndrome and autism "really" in the same spectrum?**

Clinical features:

Asperger syndrome

- 4 **Asperger syndrome** according to ICD-10/DSM-IV is nothing but autism without criterion II and a guarantee that everything was alright until after 3 years of age
- 4 This is not consistent with experience or research
- 4 Asperger's own cases did not meet criteria for his disorder

Clinical features: Asperger syndrome

- 4 **Asperger syndrome according to Gillberg (based on Asperger's original descriptions)**
- 4 **I. Social impairment - extreme egocentricity**
- 4 **II. Narrow interest pattern**
- 4 **III. Routines and rituals**
- 4 **IV. Speech and language peculiarities**
- 4 **V. Non-verbal communication problems**
- 4 **VI. Motor clumsiness**
 - Gillberg & Gillberg 1989, Gillberg 1991

A graphic of a spiral-bound notebook with a silver metal spiral on the left side. The notebook is open to a blue page. The text is written on this page.

Clinical features: disintegrative disorder

4 Starts after 3 years - very rare



Clinical features: atypical autism (PDD NOS)

- 4 Similar symptoms but does not meet criteria for childhood autism, Asperger syndrome or disintegrative disorder
- 4 Probably "overdiagnosed" in the US
- 4 Atypical autism not as often diagnosed in the UK as PDD NOS in the US?

What the epidemiological studies have shown us (for a long time...)

- 4 **Prevalence** much higher than believed in the past: ASD in 1% of population, AD in 0.2%, autistic features in 3.5% (!)
- 4 Associated with **mental retardation** 15-40% (80% in autistic disorder/AD)
- 4 Associated with **epilepsy** 5-15% (35% in AD)
- 4 **Medical disorder** in 7-17% (25% in AD)
- 4 Skewed **male:female ratio** 2-4:1
- 4 High rate of **visual, hearing and motor impairments** (including at birth)
- 4 **Sibling rate raised; identical twin rate much raised** in classic autism

Psychiatric associated problems ("comorbidity"/co-existence)

- 4 **ADHD**
- 4 **Tics (including Tourette syndrome)**
- 4 **DCD**
- 4 **Hyperlexia**
- 4 **Depression and anxiety (though not disorder?)**
- 4 **Bipolar disorder**
- 4 **Selective mutism**
- 4 **Eating disorders**
- 4 **Sleep disorders**
- 4 **"Personality disorder"**
- 4 **Schizophrenia / catatonia**

”Comorbidity”

- 4 **The overlap with DCD and ADHD is considerable**
- 4 **Children with severe DAMP (severe DCD with severe ADHD) usually have marked autistic features**
- 4 **The majority of those with Asperger syndrome have ADHD features**
- 4 **Some children ”start out” as ADHD and then ”become” typical ASD**
- 4 **Others show ASD early in life and have ADHD at follow-up**
- 4 **ADHD and ASD occur in the same families**

Genetics

- 4 **Sibs affected in 3%: core syndrome**
- 4 **Sibs affected in 10-20%: spectrum disorder**
- 4 **Non-identical twins affected in 0-3%**
- 4 **Identical twins affected in 60-90%**
- 4 All of these findings refer to probands with autism proper, not spectrum disorders
- 4 **Several genes act in concert in most cases**

Genetics

- 4 **First-degree relatives** increased rates of affective disorders, social phobia, obsessive-compulsive phenomena, and "broader phenotype symptoms"
- 4 **First-degree relatives** also show possibly increased rates of learning disorders including MR, dyslexia and SLI

Genetics

- 4 Genes on certain chromosomes (e.g. 2, 6, 7, 16, 17, 18, 22, and X) may be important (according to genome scan studies of sib-pairs)
- 4 Translocation cases important
- 4 Clinical findings in particular syndromes such as partial tetrasomy 15q, and Angelman (15q), tuberous sclerosis (9q, 16p), fragile X, Turner, Rett (X)
- 4 Neuroligin genes on the X-chromosome important in some cases

Associated medical disorders

4 **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, Herpes and rubella infection, Landau-Kleffner syndrome

Associated medical disorders

- 4 **Known medical disorders** 25% in autistic disorder "proper" (unselected samples) and 5% in Asperger syndrome
- 4 These are either **genetic** in their own right, affect autism susceptibility gene areas, or cause brain lesions through direct/indirect insults
- 4 High rate of **pre- and perinatal risk factors**

Associated medical disorders

4 High rate of gastrointestinal problems

4 Could be due to

- Unusual food/feeding habits
- Unusual motor habits with unusual bowel movements
- Specific metabolic disorders
- Gastrointestinal disorders

Rett syndrome and ASD

4 Rett syndrome

- Preserved speech variant of Rett syndrome may be behaviourally indistinguishable from classic autism in young girls
- Some girls and boys with the MecP2 gene have "only" autism (more often "regressive" variants?)

Landau-Kleffner/ESES and ASD

4 Landau-Kleffner syndrome and Electrical Status Epilepticus during Slow sleep

- "normal" for 2-18 (?) years
- Swift regression of language comprehension and partial/total loss of spoken language ("verbal auditory agnosia")
- Preserved visual skills
- Autistic type regression in many cases
- Epileptogenic discharge on EEG/epilepsy

Psychosocial interactions

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

Psychosocial interactions

- 4 Abnormal child triggers unusual interactions
- 4 Some parents have autism spectrum disorders themselves - sometimes a major problems, occasionally a major asset
- 4 Anxiety, violent behaviours, self-injury and hyperactivity reduced in autism-friendly milieu

Brain basis

- 4 **Clinical finding:** **macrocephalus** common (Bayley et al 1997, Gillberg & deSouza 2002, Zappella 2005)
- 4 **Acquired brain lesions** implicate temporal, frontal, **fronto-temporal** and **bilateral dysfunction** in core syndrome; right or left dysfunction in spectrum disorder (Gillberg & Coleman 2000, Coleman 2005)
- 4 **Autopsy data** suggest: **amygdala, pons and cerebellum** (Bauman 1988, Bauman et al 2006)

Brain basis

4 Brainstem damage suggested by

- Thalidomide (Strömmland, Gillberg et al 1994)
- Moebius syndrome association (Gillberg & Steffenburg 1997)
- Auditory brainstem responses (Rosenhall, Gillberg et al 2003)
- Decrease in/lack of postrotatory nystagmus (Ornitz, Ritvo 1967)
- Aberrant muscle tone and concomitant squint (Gillberg & Coleman 2000)

Brain basis

4 Cerebellar dysfunction suggested by

- **Autopsy** studies (Bauman et al 1992, Bayley et al 1999, Oldfors, Gillberg et al 2000, Weidenheim, Rapin, Gillberg et al 2001, Bauman et al 2006, Rodier 2006)
- **Imaging** studies (Courchesne 1988, 2006)
- Relationship to **ataxia** (Åhsgren, Gillberg et al 2005)



Brain basis

4 **Frontotemporal** brain dysfunction suggested by

- Autopsy studies
- Functional imaging studies
- Neuropsychological studies
- Combined neuropsychological-neuroimaging studies
- Clinical picture

Brain basis

4 Neuropsychological studies show

- Non-verbal learning disability in AS
- Verbal learning disability in AD
- Metarepresentation problems
- Central coherence problems
- Procedural (complex) learning deficits and decreased neural connectivity
- Mirror neuron dysfunction (frontal lobe pars opercularis)
- Superior fact learning
- Eye-tracking peculiarities, eye direction detector impaired
- Facial expression recognition impaired in children and adults, in AS and AD; drive for looking at lower face (fusiform gyrus)
- Theory of mind in the eyes impaired
- Executive function deficits

Brain basis

4 At least four **biological** variants of autism?

- **Early brainstem/cerebellar** associated with severe secondary problems (“classic autism” with MR, language dysfunction and major perceptual problems)
- **Midtrimester bilateral frontotemporal lobe dysfunction/damage** (“classic autism”)
- **Uni- or bilateral frontotemporal variation** in high-functioning cases/AS
- **Multi-damage autism** (severe handicap with MR, motor, hearing, visual impairment)

Brain basis

- 4 Likely that **several functional neural loops are implicated** and that all impinge on (social) neurocognitive functions that are crucially (but possibly not specifically) impaired in autism (Gillberg 1999, Gillberg & Coleman 2000, Coleman 2005)
- 4 **Exaggeration of male phenotype - testosterone?** (Gillberg 1980, Wing 1980, Gillberg 1992, Baron-Cohen et al 2002, Baron-Cohen 2006)

Brain basis: neuropsychopharmacology - the first studies

- 4 Dopamine (Gillberg et al 1987)
- 4 Serotonin (in MR also) (Coleman 1976)
- 4 Noradrenaline (Gillberg et al 1987)
- 4 Neurotensin (Jamain et al 2003)
- 4 Glycine, GABA, Ach, glutamate (Carlsson 2002)
- 4 GFA-protein (Ahlsén et al 1993)
- 4 Gangliosides (Nordin et al 1998)
- 4 Endorphines (Gillberg et al 1985)
- 4 Immune system (Plioplys 1989)

The pathogenetic chain

- 4 **Genetic or environmental insult**
- 4 **Damage or neurochemical dysfunction**
- 4 **Social neurocognitive functions restricted** (procedural learning, metarepresentations, central coherence, looking at upper face, executive functions)
- 4 **Superior fact learning**
- 4 **The "syndrome" (or, sometimes, the "arbitrary" symptom constellation) of autism**
- 4 **Two syndromes (Social-communicative and Behavioural)?**
- 4 **Three syndromes???**
- 4 **Dozens of syndromes**

Implications for treatment

- 4 Individualise for all people with ASD
- 4 If known underlying disorder: treat this (and be aware of syndrome-specific symptoms such as gaze avoidance in fragile X)
- 4 If epilepsy: treat this (however, there are major caveats here)
- 4 If hearing, vision, or motor impaired: treat these
- 4 Psychoeducational measures
- 4 Applied behaviour analysis (“ABA”) - also known as Cognitive behaviour therapy (“CBT”) when used with more high-functioning individuals (“early bird”?)
- 4 Symptomatic biological treatments (diets and meds)

Clinical psychopharmacology of autism

- 4 Only dopamine antagonists (neuroleptics) have been convincingly shown to affect core symptoms of autism (van Buitelaar 2000, McCracken 2002)
- 4 Risperidone and olanzapine (and haloperidol) supported by studies
- 4 SRIs supported by studies on adults (high-functioning) with AS and AD
- 4 Some support for fluoxetine in children with AD and bipolar disorder/familial bipolar disorder
- 4 Stimulants for AD/AS with ADHD and IQ>20
- 4 Antiepileptics in some cases with autism and epileptogenic discharge
- 4 Steroids in autism with regression? (Landau-Kleffner)
- 4 Role of diets? No one diet helpful for more than a small minority
- 4 Role of fishy oils??

Implications for treatment

- 4 Physical exercise!!
- 4 “Sensory awareness environment” (reduce noise, certain sounds, smell, staff knowledgeable about autism)
- 4 “autism-friendly” environment (everybody knows “all there is to know” about autism)
- 4 Concrete, visual (not always), straight-forward education (TEACCH)
- 4 ABA
- 4 PECS
- 4 Minimize ambiguities and symbolic interpretation

Outcome

- 4 Very variable; huge difference between some “low-” and certain “high”-functioning cases
- 4 Better with early diagnosis
- 4 Majority probably live to be old, but increased mortality in subgroup (with epilepsy or other medical disorder, drowning, accidents)
- 4 Basic problems remain, albeit modified
- 4 High rate of secondary psychiatric problems (personality disorder, affective, social, catatonia)
- 4 Clinical cases of AS have socially similar outcomes as those with AD, in spite of high (and sometimes “increasing”) IQ

A graphic of a spiral-bound notebook with a silver metal spiral on the left side. The notebook is open to a blue page. The word "Outcome" is written in orange at the top left of the page. Below it, a horizontal line separates the title from a list of four subgroups. Each subgroup is preceded by a yellow number "4".

Outcome

4 Four subgroups

4 Chronically withdrawn

4 Active but odd

4 Passive and “friendly”

4 Overly stiff and formal

Outcome

- 4 No language (communicative speech) before 3 years - usually AD
- 4 Some language (communicative speech) at age 3 years - often AS
- 4 No language (communicative speech) at age 7 years - always AD

The future

- 4 Specific knowledge (including genetic) and treatment for subgroups
- 4 Symptomatic treatments
- 4 Psychoeducation and applied behaviour analysis
- 4 Acceptance and attitude change! “Spreading the word about autism” (TV, radio, newspapers, books, booklets, leaflets, education of “normal” children in schools
- 4 People with autism, not autists or autistic people!
Cannot be stressed enough
- 4 Respect!

Literature

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