Autism in Boys and Girls, Women and Men Throughout the Lifespan

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Introduction

Autism Spectrum Disorder is the current name of a clinical syndrome. It is characterized both by two important communalities and at the same time an incredible variety of clinical pictures that in each individual changes over the lifespan.

The communalities, the Triad of Wing, were named after a research pioneer in the field of autism, Lorna Wing, who was an eminent clinician, scrupulous and perseverant scientist and mother of a daughter with pronounced autism. The seminal characteristics were included in the Triad of Wing that form(ed) the backbone of the DSM and ICD classification systems:

1. Impairment in the quality of social interaction (later named "in the development of social reciprocity").
2. Abnormalities in the use of speech (later: Impairment of development of language and communication).

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3. Elaborate routines, overall patterns of interest and abnormalities in symbolic imaginative play (later restricted patterns of behaviour and interest and repetitive stereotypies.

In the most recent classification, the DSM 5, the first two dimensions have been merged because research showed that they are indiscernible: one cannot imagine having greatly impaired social relationships with normal speech and communication skills and vice versa.

In first instance this Triad of common dimensions in autism was distilled from the analysis of the cases Lorna Wing and her colleague Judy Gould (1979) found when making a cross-sectional study of the population of the London borough Camberwell (with roughly 100,000 inhabitants). This marked a turning point in the history of autism after decades of parental blaming after the two independent and seminal papers in the 1940s by Leo Kanner (1943) and Hans Asperger (1944). In retrospect Kanner and Asperger described children that all had the syndrome of what we now call Autism Spectrum disorder. They seemed to have described two sides of the same coin. Kanner's patients (mainly boys) were aloof in their social interactions and had either no speech, or abnormal speech e.g. direct or delayed "echolalia" (repeating what had just been said, directly or after some time, out of the context). Kanner's children had a pronounced developmental delay, with sometimes surprising islands of abnormally brilliant functioning (especially in the area of memory or routine computing). Finally they had very good visuospatial skills and demonstrated strong motor stereotypies despite pronounced motor handiness. Asperger by contrast described only boys that were passive or active, but odd in none reciprocal social interaction; their language skills were elaborate, but only used for one-sided conversations. They were intelligent though often disharmonic in their profiles (high verbal scores versus poor performance scores) and very clumsy when it came to their motor skills. At first glance very different, but both described under the term "autistic": Kanner "Autistic disturbances of the social affect", Asperger "Autistic psychopathy".

Developmental (Psycho)Pathology

An important notion is that autism spectrum disorder is a developmental disorder. So before looking into the developmental aspects of the clinical presentation and its pitfalls, let us take a closer look into developmental disorders as their mechanism is of importance for understanding autism

spectrum disorder, its potential causes and what affects it causes during the lifespan.

Dante Cicchetti and the late Cohen's (1995–2016) books on developmental psychopathology offer an important insight in the underlying mechanisms of development. Development in humans can be conceived as an ongoing transactional process of interplay between nature (the genetic material at the conception) and nurture (all psychological and social influences). Gender is an interesting third dimension. On the one hand gender is a biological fact. This is an important determinant of behavioural and emotional coping strategies and reaction patterns. Also parents play an important role as they act and react in a different way to boys as compared to girls. In the case of autism this translates as follows: biologically (as an evolutionary outcome) females are more social than males (Brody 1999). Thus even in autism, girls will try harder to get in contact with others. Externalizing behaviour (angry and aggressive) as mostly displayed by boys, is far more challenging and difficult to manage for parents and teachers than internalizing behaviour (shy, withdrawn and anxious). In a later paragraph we will see that such differences may act as masking factors that delay the diagnoses ASD in girls as compared to boys. Thus gender is an important component in the developmental interplay (van Wijngaarden-Cremers 2015).

So what about nature? Each individual starts off with a unique genetic material wrapped up in forty-five chromosome pairs and in addition two sex chromosomes (XX for females XY for men). The genes are the genetic codes spread out over the chromosomes. Yet as from the first cell division after the conception, external influences play a role, and so do accidental miscopies during the incredible cell proliferation throughout embryonic and post partum life. This implies that even identical twins, despite extremely strong alikeness, will as from the conception develop in very different ways. The likelihood that they will have the same features or develop the same conditions is called "concordance". For many physical characteristics, the concordance between identical twins will be 100%: this holds true for the colour of their eyes, their skin complexion etc. When it comes to communicable disease the concordance rates drop dramatically. For most conditions, such as cardiovascular diseases, diabetes, high blood pressure, depression, schizophrenia and anxiety, the concordance levels are below 50%. Interestingly for neuropsychiatric conditions such as Attention Deficit Hyperactivity Disorders the concordance is well above 50%, and for autism spectrum disorders it attains its highest with 90%. Thus it can be said that it is not the disorder that is inherited but there is a heightened vulnerability to developing a disorder. The development and course of the condition into an

impairing disorder is complex because along with genetic vulnerability, different external factors play an important role as from conception. This creates difficulties for the predictive validity of ASD measures (Fig. 1).

The first level is the genotype (the genes). Between that level and the phenotype (how the person presents in social encounters), a number of "hidden" levels can be discerned.

The second level is that of the "epigenetic" alterations of the genetic make-up. The genetic expression can be altered by "mutations" (small changes in the coding). These mutations can occur just by chance (spontaneous mutations), by transcription errors or caused by external toxic agents (radiation, infections, drugs, hunger). Thus the vulnerability for e.g. autism can be innate or acquired.

The (epi)genetics determine embryogenesis. This process is a speedy individual pathway from protozoa, via a fish stage to a little human after twelve weeks. In this first trimester of the embryonic development the "wiring" of the brain occurs through differentiation and migration of neuronal material. Obviously during these weeks the development is extremely vulnerable to external agents as defined before. It is known that rubella can have a lasting effect when the maternal infection occurs around the 7th–8th week of gestation.

The brain is a dynamic organ and its functioning is highly interactional e.g. every human being is born with a capacity for developing language and

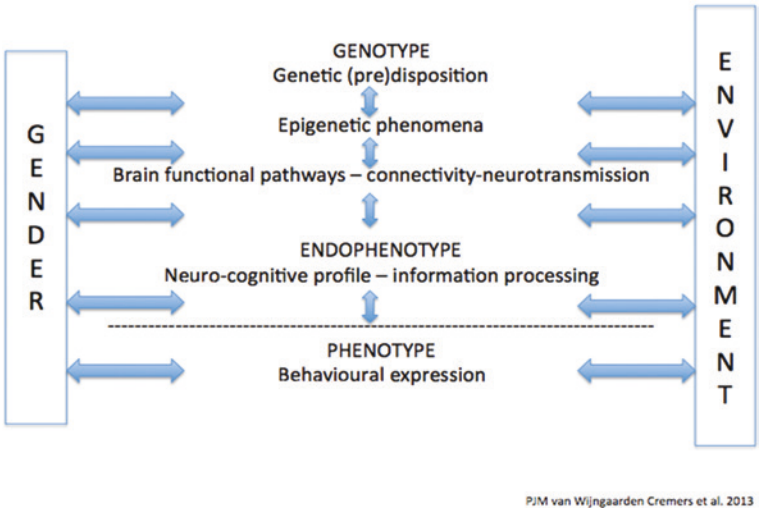

Fig. 1 The interplay and the cascade of developmental features

speech, but these parts of the brain will only develop if there is hearing perception and auditory input. A large body of research into structural causes of autism has yielded only few consistent findings, namely significantly bigger brains and fewer Purkinje cells in the cerebellum (Hampson and Blatt 2015). Both these findings can be related to less efficient information processing. More recently, new brain imaging techniques have revealed that in autism more primitive connections (local connectivity) remain active whereas in typical individuals the brain gears up to far more efficient information processing modalities that enable quick and flexible adaptation. In autism the rigidity in behaviour and habits can be explained by their brain sticking to slow, and far less efficient information processing strategies especially in the social domain. The impaired social information processing shows also in deviant profiles of neuropsychological functioning. Firstly, the overall level of functioning as measured by IQ tests in ASD shows a broad variation (ranging from severe learning disabilities up to scores far above the average). But in nearly all cases the profile of the intelligence is highly disharmonic, with roughly two extremes: in the more Kanner type individuals with autism the verbal IQ is far lower that the performance IQ whilst in those with the more Asperger type of autism, the contrary holds true.

How do these disharmonic profiles translate into neuropsychological abilities? In at least three domains of neuropsychological functioning, individuals with ASD show poor performances (Rajendran and Mitchell 2007):

1. The Theory of Mind refers to one's capacity of understanding others' minds and being able to inhibit one's own point of view to take into consideration the other's perspective. A vast body of research shows that individuals diagnosed with autism, regardless their overall ability, are slower in developing this capacity and often never really get it right.
2. The Central Coherence refers to an individual's capacity of discerning crucial details from irrelevant features and of seeing the global picture instead of a multitude of details. Here again individuals with autism, characterized by their strong "local connectivity" as described earlier, tend to latch onto details and have difficulties in getting the overall picture right. So where typical individuals get the whole picture at glance and may focus on details in second instance, individuals diagnosed within ASD tend to proceed the other way round (they focus on all the trees and it takes them time to realize that all these trees together for a wood/forest).
3. Executive Functions: this is the overarching name for capacities steered by the frontal lobes of the brain that enable individuals to plan and organize their behaviour and adapt to changing circumstances. By just defining

this neuropsychological asset, it becomes clear that individuals with diagnoses within the autism spectrum will have great difficulties with these. They tend to be rigid, detail focused and incapable of anticipating others minds and actions. This makes them anxious because they cannot anticipate much of what happens to them.

Does This Insight into Developmental Psychopathology Reveal Solid (Biological) Markers for Autism Spectrum Disorder?

So does this view of developmental psychopathology help us to identify underlying markers of ASD? Many researchers had hoped for that to be true. Every time an abnormality was found to be thought specific for autism, this finding was followed by disappointment. Deviant patterns can be discerned, but at the current stage of our knowledge these factors are by no means specific to autism or any other form of (developmental) psychopathology. A deviant gene is by no means specific. The same genetic vulnerability can express itself a series of seemingly unrelated conditions, as for example autism, schizophrenia, depression, bipolar disorders, ADHD etc. Likewise the dysfunctional connectivity patterns found in individuals with autism that distinguish them significantly from normal controls and individuals with learning disabilities are by no means specific for autism but can be found in the other disorders listed here above and even in healthy individuals. The same holds true for the neuropsychological dysfunctions.

So further understanding of the impact of environmental factors is crucial in order to understand why specific vulnerabilities can lead to such different outcomes in a clinical sense. Understanding the impact of gender is crucial too. We know (van Wijngaarden-Cremers 2015) that under the same kind of environmental stress, males will tend to develop very different pathology than females e.g. men will react with high blood pressure, gut problems or a lowered threshold for infectious disorders, whereas women will develop depression and/or autoimmune conditions (Goel et al. 2014).

In summary, in the field of development of non-communicable diseases many questions remain still to be addressed. At this stage we must conclude that there is no construct validity to underpin the diagnosis of autism spectrum disorder. The predictive validity is weak (in terms of predictable outcome). Although the "face validity" of a distinct clinical syndrome is very strong (Lord and Jones 2012), but the clinical expression of impairments in

terms of clinical symptoms is very broad. In the next paragraph we will look into this diversity along a series of different dimensions.

Differences in Phenotypical Expression in ASD

In the previous paragraphs we have made it clear that ASD is a complex developmental disorder. It can be perceived as a definite clinical syndrome with a large range of symptomatic expressions along the dimensions that define it (Triad of Wing). We have also seen that the symptoms can vary in their expression according to gender and change as development progresses. In this paragraph I will discuss the different types of clinical expression and underscore in each of the gender differences and changes of time as far as known.

Which are these dimensions? Wing and Gould (1979) defined a series that still prove helpful when assessing patients:

1. Impairments of Social Interaction.
2. Impairments of communication.
3. Impairments of Imagination (better translated as "of Thinking and Behaving").
4. Abnormal responses to stimuli.
5. Extreme emotional expressions and inadequate behaviours.

1. Impairments of Social Interaction: originally three expressions were distilled from the big group of individuals in the Camberwell Study (1979) (aloof, passive, active but odd). Later "over-formal and stilted" was added.

- The "*aloof*" expression is the first group of impaired social interaction: according to the Oxford dictionary the adjective "aloof" refers to conspicuously uninvolved, cool and distant. The term was first used by Leo Kanner to describe the deviant quality of the affective contact. Aloofness is for many lay people the main characteristic of autism. But in autism research it is generally only seen in very young children. As it is a prominent and impressive feature it is obviously one of the first signals that raises concerns and signs in detecting autism in very young children. For parents "aloofness" in their baby is puzzling and frustrating. Oftentimes these children are suspected of having severe visual of hearing impairment, as they do not seem to react at all to their environment. Frustrating for parents mainly in the sense that it puts them off. Studies (Dawson 2008; Wan et al. 2012; Green et al. 2015)

have shown that there is a limit to parents stimulating verbal engagement if their child does not respond and encourage them by responding with attention and eventually a rewarding smile or laughter. Avoidance of eye contact fits into aloofness. These children do not respond to spoken language, do not engage into joint-attention and seem utterly insensitive to cuddling. They are often described as living in a world of their own. Fortunately "aloofness" tends to fade away during the natural course of development in which even children with pronounced autism and marked initial aloofness seem to "defrost" and become more open to contact.

In terms of *gender*, aloofness is associated with extreme autistic aloneness encountered in very young children, and especially girls with a pronounced developmental delay. In high-functioning ASD girls and women it is seldom seen, as they tend to be more eager, though clumsy in trying to engage in social interaction.

In terms of *development*, "aloofness" tends to fade away, but can persist in association with (marked) learning disabilities (Wing 1996; Beadle-Brown et al. 2002).

- The "passive": This variant is characterized by the fact that the individual themselves does not engage in social contacts, but may open up and engage in some interaction if cautiously and adequately approached by adults that manage to keep the stress levels low. In these children the gaze avoidance is lesser, they may eventually make eye contact and engage in joint activities. These activities are mostly more in parallel than truly interactive and in a reciprocal way.

  From the point of view of *gender* the passive disengagement in girls is often misperceived as "shyness". Being shy fits into the perception of girls by parents. Parents with daughters that are "passive" tend not to worry as much as parents of boys with the same type of behaviour that are alarmed by the lack of initiative that they attribute to boys.

  In terms of *development* the "passive" expression fits into the "natural" course of development. Often aloof children, turn into passive at the end of their childhood and often become "active but odd" as adolescents and adults. It is often this changing variation of awkwardness in social interaction that makes them seem so very "different". The late Sula Wolff (1995) described this condition extensively in a book on her studies of this group under the well-chosen title "Loners".
- The "active but odd": This variant of impaired social interaction seems a kind of paradox. Why? Because people with this "active but odd approach" do make contact with others but their approach is blunt and

inappropriate. They may approach others with questions that may look impertinent. Or tell unasked stories about their interests of preoccupations. The inappropriateness lays in the fact that their approach is one-sided. There is no mutual reciprocity. The eye contact may be poor, or often too prolonged. The oddity may extent to shaking hands or hugging too hard. In *females* this may wrongly be interpreted as a desire of opening to sexual intimacy, which can make them vulnerable to abuse.

- In boys it may also be complicated; let us illustrate this with a clinical case:

> Ivan is the only child born to his parents who were already older when he was born. His then 62-year-old dad was a successful banker with a touch of eccentricity, whereas his mother was a teacher in Latin and Greek. They met at a computer hobby group. For both it was the first really meaningful relationship. As a boy Ivan was fascinated by vinyl disks with displays on them and his parents indulged this peculiar hobby and travelled great distances to attend auctions. At elementary school he was strangely popular because he knew every thing and could talk about it in an entertaining way. He played the clown to make people laugh at his clumsiness. Basically he was a loner that was handy at computer hacking as from a very young age. As an adolescent he ran into trouble on various occasions because he assaulted girls and women sexually, ignoring in a most indecent way what they said or did, merely following his sexual urges and gaining great satisfaction from this indecent behaviour. As a student in informatics he would show off by hacking a big company or a bank. When he hacked the headquarters of N.A.T.O by means of curiosity, he was arrested. During the trial he pretended being a spy. In prison he was finally diagnosed with autism. Strangely but partly understandably he loves being in prison, and as soon as he is released does anything, from hacking, to robbing violently without any remorse elderly people, in order to be able to return to prison. His recurrent behaviour is a nightmare for his mother and an inextricable puzzle for professionals.

This case illustrates several aspects of ASD in boys and men. First case of elder parents: It appears that autism occurs more frequently in elder fathers but also mothers. Often these parents tend to be more indulgent towards the behaviour of their little boy, who in consequence is insufficiently corrected, when he with his odd behaviour violates other children's boundaries. Secondly the lack of empathy of a male with autism can influence in an awkward manner their attitude towards others, especially women and sex. Autistic men tend to report gaining more satisfaction from intimate relationships than autistic women. The latter tend to make wrong interpretations of men's desire, assuming that they long for an intimate relationship and not merely to use them for sex (Byers et al. 2013a, b). Finally in men

with ASD their potential "psychopath" like aggression and callousness that makes them to be overrepresented yet not always acknowledged in the incarceration system (BMJ 2016).

The "over-formal and stilted" expression is seen in individuals with autism that try hard to relate. Often girls and women show this very formal excessively polite way of interacting. They tend to stick to the rules of social interaction very hard, unfortunately without the result they hope for namely making acquaintances and friends. This style can also be seen in high-functioning men with a slightly pedantic style as described by Hans Asperger (1944) both in his patients, and their fathers. Asperger alluded to the fact that many of his patients had bright fathers, often professors in theoretical subjects. Baron-Cohen refers to the overrepresentation of engineers amongst the fathers of patients with Asperger's and confirmed this hypothesis by showing that in high-tech places like "Silicon Valley", his own university town Cambridge and Eindhoven the cradle of the technical multinational Philips the prevalence of ASD is much higher than in the general population. This led Baron-Cohen (2009–2011) to formulate the "autism as a defect of empathizing and the extreme male brain" hypothesis, with the complementary explanation that females with ASD had been exposed in the womb to higher levels of testosterone as usual.

2. Impairments of Communication.

In a number of very young boys and girls with severe autism and a marked developmental delay, spoken language may never develop. But in most individuals on the autistic spectrum there are peculiarities and oddities in "using speech" that should be noted:

- "Using speech"
  - Echolalia, repeating words or sentences immediately, or later out of the context, after the other has uttered them. This is a normal developmental feature in young children in their second year of life, when they acquire and practice spoken language. In individuals with ASD it may persist far longer, sometimes well into adulthood.
  - The phenomena of "delayed echolalia" may be misleading. Adults unfamiliar to the child can be in first instance amazed by the "adult like" elocution in young children that out of the blue produce the most beautiful sentences.
  - Another particularity in using speech can be palilalia. This is the involuntary repetition of syllables, words or phrases.

  - These three speech abnormalities occur often in people with ASD but can also be encountered in individuals with developmental delay, without autism.
  - Other speech peculiarities include: answering questions in a far too detailed manner. Or omitting "linking words" as e.g. 'because' or "joining words" that are part of the pragmatics of language and are necessary to help the other understand the context and sequence of what one wants to tell. In sum, individuals with ASD are not good at "tuning into the listeners' needs", a capacity that is utterly important in conversation.

- "Pragmatics". Using and understanding non-verbal communication. Along with using specific "linking" and "joining" words, pragmatics of communication include usage and understanding of facial expressions and gestures. Individuals with ASD lack both these pragmatic skills or may use them in a clumsy or unnatural manner. This holds true especially for girls and women.
- "Understanding speech". Most children with autism do develop understanding of spoken language, sometimes through additional visual cues or by singing instead of uttering. Difficulties may arise when words sound very much alike, but the biggest problems children and adults encounter with understanding language comes from the fact that they tend to stick to the literal meaning. They therefore experience great difficulties in understanding sarcasm and getting jokes.
- A variant to the previous point is the incapacity to lie or deceive, expressed in an extremely naïve honest way of telling.
- Pitch of voice and Intonation: modulation of tone and pitch are essential in human conversations. People with autism tend to express themselves in a monotonous and often loud and mechanical fashion.

3. Restricted, repetitive patterns of behaviour, interests, or activities, "Impairments of Imagination" and abnormal reaction to stimuli.

As in many of the differences in expression of symptoms of autism, when it comes to imagination it is either too little or too much. In individuals who lack imagination the problem is that they tend to take every thing literally and cannot anticipate, because they cannot imagine what is about to happen. On the contrary if they have too much imagination, they get carried away and imagine the worst. In both cases the normal function of imagination, that is to help anticipate what could happen and work through what has occurred, is missing. This was dropped as a separate domain as the

lack or overflow of imagination is best understood too as an expression of defective regulation of basic functions.

So before entering into details of the expression of the regulation systems, let us describe them and looking into gender differences in the process: in individuals with ASD we often encounter remainders of primitive affect regulation in very young children: flapping with excitement, rocking to sooth down, putting things in a specific order, special interests in particular topics car brands in boys and horses and ponies in girls. These activities are meant to regulate arousal: both stimulating when bored or to calm down when too excited or anxious.

Regulation of their arousal is a challenge that individuals with autism solve in two different but functionally linked manners. The first is through the soothing effect of:

- Motor stereotypies: these can vary from
  - Repetitive movements: like flapping, rocking, spinning one self or objects
  - Sticking to early childhood routines like smelling, tasting, bringing objects to their mouth.
  - Engaging in more complex ritual routines like placing object in lines or sorting them.
  - Getting in trance by listening to or watching spinning machines.
- Focusing and getting heavily preoccupied.
  - This can range from bizarre obsessions with dinosaurs, historical figures, nature, timetables and the weather, dates or clear operations like knowing all the prime numbers, or developing incredible multiplication or other mathematical skills.
  - In females the confusion can stem from the fact that their preoccupations are less bizarre and often near normal. In girls: horses and ponies, preservation of the environment, concerns about the future of the planet or involvement in (romantic) literature.
  - Preoccupations that were functional at a young age may in the course of development turn into dysfunctions, obsessions and compulsions after puberty. Sometimes preoccupations are not easily recognized. For example “transgender” feelings and ideations are far more common in

individuals with ASD than in the general population (de Vries et al. 2010). When looking into it more closely, the preoccupation with gender identity may reflect uneasiness with sexual maturation and identity in general more than the genuine feeling of living in the wrong body.

Abnormal response to stimuli.

This very important feature, described both by Kanner and Asperger and observed by Wing and Gould in the Camberwell study, was not included in DSM until DSM 5, and appears in one way or the other in nearly every individual with ASD.

- Hypersensitivity: people with ASD may be oversensitive to sound and noises (including some pitches of voice), light and colour, texture of clothing, interior design or architecture but also to being touched, cuddled, kissed or merely being looked at.
- Hyposensitivity: individuals with ASD can be (relatively) insensitive to heat and cold, but also to pain. This can lead to medically dangerous situations, when they sense no pain in life-threatening situations like appendicitis, injuries, burns or malignant diseases.

It may be extremely confusing when a person with autism has both hyper- and hypo-sensitivities e.g. the person that gets angry at every noise in the central heating system, can easily get scolded when taking a shower without noticing.

When even their "strange" arousal regulation systems fail to help them cope with situations that are stressful for them it is not unusual that they get extremely upset and experience extreme emotions (blind panic) or tantrums. ASD boys can become extremely aggressive and perform challenging behaviour towards objects but often too against people, in particular the most near and dear ones. In ASD girls/women this can lead to self harm and suicidal behaviour This behaviour in individuals with ASD is often misperceived by others and labelled as "challenging" or "provocative", whereas it is most often "reactive" to unexpected changes, confusion, or overload with stimuli. So the solution is to address both the behaviour and the environmental triggers to the behaviour. For example, the person with ASD that can be taught to signal hyper-arousal before it becomes overwhelming.

Late Diagnoses in ASD (in High-Functioning Individuals)

Clinical picture/vignette

Mary was 22 years old when she was first referred to our clinic. She had already had several unsuccessful treatments in addiction clinics before entering our clinic for the treatment of Substance Use Disorders (SUD), Post Traumatic Stress Syndrome (PTSS) and borderline personality disorder. She was addicted to heroin, cocaine and also used cannabis, ecstasy, speed and alcohol on a regular basis. She started using drugs when she was 14 years old. Her father had physically abused Mary. At the elementary school she had aggressive outbursts, which disappeared at the age of 10. At the same time a 16-year-old boy from the neighbourhood began sexually abusing her. Later, in high school, she also was sexually abused by one of her teachers. After detox, Mary was a very anxious, shy, chaotic, restless and clumsy young woman who had difficulties expressing her self in the group. Though she did not interact much with the group, she was not a real loner. The group members instantly liked her. One poignant habit of Mary's was to take showers several times a day. Both her shyness and her frequent showering were interpreted as a consequence of her history of sexual abuse. During her treatment in our clinic, we did not observe any symptoms to confirm the diagnosis borderline personality disorder. Due to her chaotic and clumsy behaviour, a hetero-anamnestic confirmed history of lifelong concentration problems and hyperactivity, we first performed a standardized clinical assessment on ADHD, which confirmed the presence of ADHD. For both ADHD and PTSD she received treatment according to our guidelines. Unfortunately, after a short period of improvement, her situation seemed to worsen: Mary became afraid of leaving the clinic and spent a great deal of time alone in her own apartment, avoiding the necessary steps to build up a social life. She became more and more anxious, with increasing insomnia and nightmares and coincidentally she developed more compulsive behaviour such as showering even more often and for a longer time than she did before. Moreover she developed a specific and strict ritual for showering. The staff observed these changes and felt increasingly concerned. On closer examination it appeared that she simply did not know how to live her life. She had gross difficulties in interpreting social situations. And new situations simply scared her off. Her lack of imagination made it impossible for her to anticipate correctly. It became clear why she had been so vulnerable for sexual abuse: she had misinterpreted the intentions of her abusers. She did not dare to say "no" because she thought that she had to comply to meet their expectations, and was also afraid to lose their friendship. Her history revealed that all these problems had been there as from her most early days. And finally after a standardized comprehensive assessment, according to the Dutch Guidelines, an ASD diagnosis was confirmed.

This vignette highlights that shyness and a variety of psychiatric symptoms may mask the ASD in women. Intelligent females with ASD appear to look carefully at what other girls of their own age do. They are eager to be accepted. And in order to achieve that goal they merely copy the other "girls'" behaviours. But whilst they think to act correctly they do not realize that all too often they miss the point. They misinterpret others' intentions which make them acutely vulnerable to (sexual) abuse. Finally it is not uncommon that they start taking drugs to overcome their fear for social encounters.

Missed and Wrong Diagnoses

It remains unclear why, in so many cases, especially in women, a condition as severe as ASD can be overlooked for such a long time. As children they go unnoticed. In adolescence problems will only start if the demands for social skills and flexibility reach beyond their capacities. Several studies showed that parameters such intelligence, a predictable environment, a series of comorbid psychiatric disorders such as anxiety, obsessive-compulsive disorders (OCD) depression or {micro}-psychoses (Kanne et al. 2009; Ragunath et al. 2011) and being female (van Wijngaarden-Cremers et al. 2014) can be considered to be "masking" factors with regard to their underlying autism.

Sometimes parents manage to cope with the ASD in their child by running very strict and well-organized households that provide enough structure in which they act as "help-egos" to their ASD child unintentionally compensating for his deficits and in the process masking the autistic disorder.

Comorbidity Patterns

Comorbidity is extremely frequent in autism spectrum disorders. Lifetime psychiatric comorbidity may range up 70–100% in patients with ASD (Rosenberg et al. 2011). These co-occurring conditions include both internalizing disorders such as anxiety, obsessive-compulsive, depression and mood swings as well as externalizing disorders such as ADHD, aggressive behaviour and disturbances in sleep and eating patterns (Rosenberg et al. 2011).

Anxiety disorders, for instance coexists with ASD in at least 30–50% of autistic subjects (Simonoff et al. 2008) in adulthood. This includes specific phobias (30%), OCD (17%), social anxiety disorder and agoraphobia (17%), generalized anxiety disorder (15%), persistent separation anxiety (9%) and panic disorder (2%) (Van Steensel et al. 2011; Kanne et al. 2009). The diagnostic confusion is caused by misinterpreting ASD problems in social reciprocity as "social anxiety", and ASD preoccupations as OCD (Kanne et al. 2009; Ragunath et al. 2011).

The frequency of depressive episodes in children with ASD appears to be extremely variable, with estimates ranging from 1.5 to 38% (including up to 10% of major depressive episodes). In contrast, the variation in prevalence of bipolar disorders is estimated only to be 2.5–3.3% (Ragunath et al. 2011).

Gender Differences

The prevalence of ASD is approximately 1% in the general population (Fombonne 2009). The overall sex ratio is estimated to be 4–5 males versus 1 woman (Baird et al. 2011). In individuals with co-occurring intellectual disability the sex ratio drops to 2:1 or tends to be equal, whereas women are grossly underrepresented in high-functioning individuals with ASD.

ASD may show a bimodal distribution in females: there is a group of severely impaired girls who are diagnosed in very early childhood. But on the other side there is a group of girls with milder or atypical symptoms that are overlooked until adulthood or often not diagnosed at all.

There is quite solid evidence that there is a specific female phenotype in autism representing severe cases of autism with co-occurring marked intellectual disability that subsequently are diagnosed early in life (Ozonoff et al. 2010; Rivet and Matson 2011). Several studies have shown that girls with milder symptoms and a normal IQ tend to be diagnosed at a later age than boys (Kopp and Gillberg 1992; Siklos and Kerns 2007; Giarelli et al. 2010; Russell et al. 2011; Begeer et al. 2013) or are systematically misdiagnosed (Kopp and Gillberg 1992; Nilsson et al. 1999; Begeer et al. 2013).

In research it is obvious that there is a very strong male bias in ASD: boys and men are overrepresented, whilst the diagnostic criteria are wrongly presumed to be applicable to both sexes (Lai et al. 2011); the DSM criteria are mainly based on male behaviour and so are the thresholds for qualifying to the diagnosis (McLennan et al. 1993; Holtmann et al. 2007; Lai et al. 2011).

When we look into the studies that focus on gender differences in ASD, the findings are inconsistent and the conclusions can be ambiguous

(Lai et al. 2011). However, once the diagnosis of ASD (according to the current criteria) has been established, studies show that there are no differences in the type or severity of the core symptoms, and the same type of comorbid conditions accompany ASD in girls and boys (Lugnegård et al. 2011; van Wijngaarden-Cremers et al. 2014). This indicates that there is a definite ascertainment bias. Females that do not meet the "male criteria" for ASD will remain undiagnosed as long as we have not been able to define the female variants for the male criteria.

Management and Course

ASD itself is a persistent problem and no treatment can cure the condition. But "prosthetic" measures and adjustments of the environment can greatly enhance the quality of life in people with ASD and help them live a valuable and happy life within their limitations.

What are the characteristics of the clinical guidelines for ASD?

In most clinical guidelines, as summarized in the recent NICE guideline both for children and adolescents (2012) as well as adults (2017), it is emphasized that specific knowledge and expertise are required in order to be able to be helpful to patients with ASD and their close relatives.

First of all an adequate and adapted way of communicating is needed. Professionals dealing with patients with ASD should know how to communicate with people with ASD and how to genuinely take their point of view and needs into account. They have to be prepared to team up with parents and/or relevant relatives, and take a comprehensive approach ensuring quality of life in all its facets.

This means the management plan should focus on:

a. Psycho-education in which the patient and parents/relevant relatives are provided comprehensive information on ASD in general, as well as specific information regarding the personalized diagnostic profile.
b. The diagnostic profile stemming from a systematic assessment should give a realistic picture of strengths and vulnerabilities as well as the risk and protective factors within and around the individual in question. These are key features and the basis of a personalized management plan.

Then the treatment plan should include:

c. Training of social skills individually or in a group.

d. Offering adequate interventions aimed at preventing or reducing challenging behaviour if present.
e. Looking into adapted living and school/working conditions being prepared to help in providing information (together with the patient) and eventually coach employers/co-workers—i.e. teachers and fellow students on ASD, and how to approach, involve and help the individual with ASD in every day life.

ASD is a lifelong condition. Services should be prepared and funded to offer ongoing support adapted to the circumstances throughout the lifespan. Likewise a program for an individual with ASD needs to be tailored to his/her individual needs and thoroughly explained to the person with ASD and all those in her/his environment. This is often one of the main reasons why it is so difficult for individuals with ASD to find a job or a meaningful daytime activity. Employers and co-workers need explanation on the specific strengths and weaknesses of this individual with ASD and learn how to read and understand her/his idiosyncrasies. On the other side, the individual with ASD and his near ones need to be coached in what is expected in the "real world", because sometimes in the sheltered home situation idiosyncrasies may have become accepted and overlooked as socially utterly inappropriate.

Future of ASD

For Research

We argue that research should take a different approach, namely targeting genes and endophenotypes at a different level, and take development and gender into account as crucial features when studying developmental {psycho} pathology, instead of sticking to behavioural categories that do not have solid and specific underlying {biological} markers.

For a better understanding of the gender issues in ASD, retrospective but also prospective studies are badly needed to help and understand how ASD presents in girls as they develop, and which factors mask the diagnosis of lead to misdiagnoses or late diagnosis. Finally, more research is needed to develop screening instruments that are better fitted to help defining and identifying a female phenotype of ASD.

For Clinical Practice

Clinicians should favour individual multilevel diagnoses above mere classifications and take gender into account. It is important that they assess the individual's environment in order to trace (gender-linked) risk- and protective factors. Clinical awareness of broader underlying categories and developmental (and gender) aspects will be of great importance.

Education and training of medical and other healthcare professionals is needed in order to help foster the change of focus from a segmented approach to (psycho) pathology with a "one-fits-all" guideline treatment approach, to a far more integrated personalized approach.

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