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Diagnostic tools for Autism Spectrum Disorders by sex: Analysis of current status and future lines

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Abstract: Studies on the prevalence of Autism Spectrum Disorders show a gender disproportion. In the last years, there has been an increasing interest in the search for an explanation. There are two main lines of research; the first one looks for sex-related biological reasons that justifies the low prevalence of ASD in women (some protective factor related to hormones or immune system among others), and the second line of studies is related to the possible biases introduced in the diagnostic tools or procedures. In this article, a review of the latter line of research is made. Theoretical analysis following two objectives: a) Analysis of possible biases in diagnostic tools and b) Other non-biological explanations for gender differences in the prevalence of ASD. The literature analyzed provides contradictory results although it evidences the possible bias both in the construction of the diagnostic tools and in the assessment and determination of their standards. It is necessary to develop specific or complementary tools and diagnostic procedures differentiated by gender in order to control for this bias.

Keywords: Autism Spectrum Disorders; Diagnostic Tools; Sex; Differential Diagnostic.

1. Introduction

Autism Spectrum Disorders (ASD) are a complex set of neurodevelopmental disorders that are defined, according to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, fifth version) [1] by two groups of symptoms: a) communication and social interaction deficits (CSID), and b) presence of restrictive and repetitive patterns of interests, behaviours and activities (RRIB). These symptoms appear already in the early stages of development, last a lifetime and manifest themselves in the most important areas of the normal functioning of the person (affective, academic, work, social, etc.), causing a clinically significant deterioration.

Evidences seem to indicate that ASD would arise from the interaction between certain genetic lability and environmental variables whose consequence would be an early alteration in brain development [2]. One of the arguments on the genetic basis of the disorder has emerged from epidemiological studies, where it is shown that there is a disproportion in prevalence based on sex, with a higher proportion of cases among males, of 3:1 [3], 4:1 [4, 5] or 5:1 [6, 7]. Differences between those studies are justified by the methodology used or by the cohort age they include, being consistent regardless of geographical origin, ethnicity, culture, etc. [8]. However, if we analyze prevalence data according to the severity of symptoms, the differences tend to decrease [9, 10]. Conversely, when the study refers to the population of high-functioning ASD (HFASD) or Asperger's syndrome (AS), the prevalence figures for sex vary significantly, reaching ratios of 9:1 or 10:1 [11, 12].

In recent years we have witnessed a significant increase in scientific, clinical and social interest that generated a body of specialized knowledge [13] that aimed to find explanations for the differential gender prevalence rate in ASD diagnosis [14]. In general, scientific literature proposes two lines of justification. First, there is a body of research that suggests that the low prevalence rate in women could be caused by protective biological factors. In this sense, genetic research often shows results of sexual dimorphism in ASD. In this line of argumentation multifactorial theory it has been postulated and proposed

that some genetic variants and environmental factors could be possibly interacting with specific characteristics of female gender (i.e. hormones, immune function, etc.), and that they could be generating some protective factors against the development of ASD [15, 16, 17, 18], relating it to steroidogenesis in utero [19, 20], with testosterone concentrations in the amniotic fluid [21, 22], or with the excessive production of androgens (in women diagnosed with ASD) [23]. Second, there is a different research line that seems to focus the reason for the low prevalence of ASD in women on the insufficient detection/diagnosis by bias of current assessment tools used for girls. In this sense, and precisely because of the high prevalence rates in men, Murray et al. [24] pointed out this bias in ASD diagnosis tools. In Kanner [25], a study this disproportion of cases was presented according to sex (of 11 cases described, 8 were boys and 3 girls), so that traditionally has been attributed to ASD a predominantly male condition, paying more attention to the characteristic symptoms that manifest the disorder in men [26, 27, 12, 28, 29], introducing important biases for women’s evaluation.

The present research is part of the second line of argument (i.e. that focuses the explanation of the low prevalence of ASD in women on the possible lack of sensitivity of the current evaluation instruments for detection/diagnosis). In this sense, the main objective of this theoretical review is to carry out an analysis of the possible reasons for the under-diagnosis of women according to both the nosological criteria and the characteristics of the existing diagnostic tools. To this end, we will divide the analysis into two major research questions that guide the line of argument that we are interested in proposing for further discussion. The first will seek to determine how current diagnostic tools may bias the female diagnosis of ASD, while the second will seek to find complementary measures that can improve the diagnosis of ASD in women. Figure 1 shows the proposed line of argumentation and two research questions with the inclusion of topics that we have selected in each case.

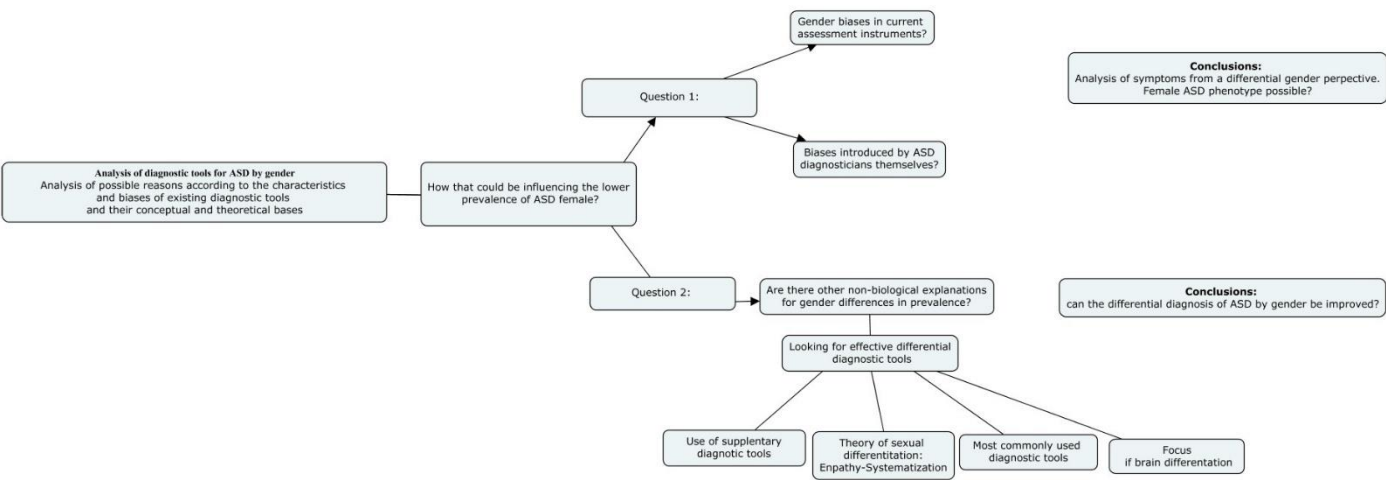


Figure 1. Outline of the theoretical analysis process.

2. Analysis of biases in methods and tools for the diagnosis of ASD in women

To answer this first research question, we will review two recent research argumentation lines that we consider of crucial importance to address the answer in a multidimensional and comprehensive manner. First, we will analyze the group of studies that have focused on ASD diagnosis and we will also review the most commonly used diagnostic tools. Secondly, we will consider the group of recent studies that have assessed the differences by sex and classify the results according to the diagnostic tools used.

Although a great research effort has been developed in this investigation area, the causes of ASD are not yet known and, at the moment, specific biomarkers has not been

clearly identified [30]. Consequently, we think that the ASD diagnostic process should be performed with information from multiple sources [31].

The diagnostic process can be said to begin when family members or professionals detect any of the possible warning signs. In general, the diagnostic process involves two paths; first, the confirmation of the symptoms detected as a warning signal and the level of severity of the symptoms and, second, the exploration or discarding of any known causes of that symptomatology. According to all the literature consulted, the diagnosis of ASD can nowadays be established stably at around 20-24 months of a child's life [32, 33, 34, 35]. In any case, the diagnosis consists in determining whether the case we are analyzing meets the most recent and complete diagnostic criteria, as those of DSM-5 [1] and ICD-11 [36].

This diagnosis process is based on three pillars [37]: (a) the child's development history; (b) the symptoms' observation and (c) the clinical confirmation. With regard to the first pillar, we must begin with an interview on the development of the child, and then complete it with the clinical and developmental history (e.g. age of appearance of the most significant developmental signs of the disorder). Second, the child's behaviour observation is a basic assessment tool, and therefore standardized systems are used in which the child performs certain games in the presence of the evaluator, so the more characteristic disorder's behaviors it can be observed, if any. Finally, after accumulating evidence about the presence of symptoms and the assessment that these symptoms significantly affect the day-to-day life of the child and his/her family, a clinical assessment is needed to confirm the existence of an ASD.

Therefore, it is important to emphasize that ASD diagnosis represents a challenge to the current disorder available knowledge, not only because of the complexity of the phenotype but also because of the diversity of forms of clinical manifestation; especially, in early ages, in less severe ASD cases [38] and in more complex ASD cases that are more frequently observed in girls compared with boys [39]. Thus, many studies confirm that the diagnosis in women is later than in men [40, 41, 42, 43], in the same way as other neurodevelopmental disorders such as ADHD (Attention Deficit and Hyperactivity Disorder) [44, 45]. The difference can be explained, in part, because in boys the behavior is in general more disturbing, with more externalizing behaviors. On the contrary, girl's symptoms are more aligned in the lack of attention and in internalizing behaviors. These difficulties on women diagnosis lead to a greater vulnerability, because is clearly related with the lack of specific early ASD interventions [13] or with erroneous diagnosis. Additionally, this under-diagnosis is increased when it comes to ASDHP or AS [46, 40, 12].

2.1. Most commonly used diagnostic tools

Among the most prestigious diagnostic used tools are the ADI-R diagnostic interview (Autistic Diagnosis Interview Revised [47, 48], which have become the "gold standard" for the ASD diagnosis. The ADI-R is a clinical interview conducted with parents or caregivers of the person suspected of suffering from ASD. The clinical interview main questions focus on three broad areas (i.e. language/communication, reciprocal social interactions, and restricted behaviors and interests). The parents or caregivers' responses are then encoded and valued using two main scoring algorithms. The first is called a "diagnostic algorithm" and assesses the complete subject's development history. The second is called "algorithm of current behavior" and it scores the behavior observed in recent months. Apart from that, the ADOS (or its current version ADOS-2) is an standardized protocol for observing social and communicative behavior and responses and behaviors are coded according to specific objectives associated with each task, rating the quality and type of response, there is evidence of its objectivity [49, 50].

Both the criteria for presentation of symptoms and the validation of both tools have been performed with excessively homogeneous samples, generally composed of mostly Caucasian men, cisgender, heterosexual and residents in the USA, Western Europe or Australia. This situation reflects a certain intrinsic tautology, given that tools for diagnosis and understanding of ASD have been developed using samples formed mainly by men

or with a low representation of women and pretended to demonstrate differences based on sex.

There are other ASD diagnosis instruments that we will review below. The CARS (Childhood Autism Rating Scale) [51, 52] is a 15-item evaluation scale designed to detect and assess the ASD symptoms and other developmental disorders. The CARS assesses different child development areas (Social relationship, Imitation, Emotional response, Use of the body, Use of objects, Adaptation to change, Visual response, Auditory response, Use and response of taste, Smell and Touch, Fear or nervousness, Verbal communication, Non-verbal communication, Activity level, Level and Consistency of Intellectual Response). Each child is evaluated in each domain on a graded scale where the highest scores indicate the highest degree of deficiency. The second edition CARS-2 [52] presents two forms, the standard and another one called CARS 2-HP (High Performance). The latter was developed as an alternative measure to differentiate individuals with verbal fluency with HPASD.

The DISCO (Diagnostic Interview for Social and Communication Disorders) [53] is an standardized and semi-structured interview for the ASD diagnosis and the subsequent design of educational and treatment resources. It consists of 362 items that collect social interaction information, communication, imagination and repetitive behaviors, as well as on other aspects necessary to know the level of support required (daily life skills, attentional difficulties, hyperactivity and challenging behaviors). The DISCO offers algorithms for the diagnosis of autism but, for its application, requires qualified and accredited personnel.

Additionally, Baron-Cohen et al. [54] developed the Autism-Spectrum Quotient (AQ). It is a self-administered instrument composed of 50 items that measure the degree to which adults with normal intelligence have traits associated with ASD spectrum. The included features are social skills, attention shift (flexibility), attention to detail and communication and imagination; and can be used as screening in adults without intellectual disabilities (ID).

Concern over the detection and diagnosis of ASD has increased the number of detection and diagnostic tools, ASD identification protocols and has evolved diagnostic criteria in order to find the best description of the ASD behavioral phenotype with all possible symptom constellations. In most cases, other complementary tools such as the Social Response Scale (SRS or SRS-2, [55, 56], the Repetitive-Revised Behavior Scale (RBS-R, [57]), the Vineland Adaptive Behavior Scale, 2nd Edition (Vineland-II, [58]), the CBCL (Child Behavior Checklist [59], and the ABC (Aberrant Behavior Checklist [60]). However, as far as we know, no specific or complementary tool has been developed to support the diagnosis of ASD in women, so the possible biases in the diagnostic tools can also be reproduced in the additional tools.

2.2.- Differential results by sex according to the diagnostic tools used

Frazier et al. [61] conducted a comprehensive study of 2,418 participants (only 304 were women) recruited from the "Simons Simplex Collection"; a core project and resource of the Simons Foundation Autism Research Initiative (SFARI), which aimed to establish a permanent repository of genetic samples from 2,600 families, each with a child diagnosed with autism spectrum disorder, and not ASD parents and siblings. The central symptoms were evaluated by ADI-R and ADOS and the complementary measures were SRS, RBS-R, Vineland-II, CBCL and ABC. The results indicated that women with a ASD diagnosis had a greater social communication deterioration, greater restricted interests, lower cognitive capacity, less adaptive capacity and greater externalization problems, than men. The study was concluded following the line of previous work [9] in which they proposed that women that receive a correct early ASD diagnose, tend to show much more salient symptoms than men, showing worse prognosis, worse social, communicative and cognitive functioning.

Tillmann et al. [62] developed another multicenter study (i.e. 18 centers in nine states of the European Union) reaching a sample of 2,139 ADI-R (376 women) and 1420 ADOS

(233 women), but the study was reduced to 1,030 subjects for which ADI-R and ADOS data were available simultaneously (38% of the sample). The results indicate that CR-IR evaluated in ADI-R in early childhood showed lower punctuations in women, while CIS levels were similar. When comparing the ADI-R and ADOS scores, no significant differences were found in the severity indexes of the disorders.

Adamou, Johnson & Alty [63] developed a study to determine the possible bias of ADOS in a clinical population. Out of a total of 43 participants (31 men and 12 women), they observed that the positive diagnosis rate in men was 38% while in women only 25%. In addition, the scores obtained by the men diagnosed were significantly higher than the ones obtained in women, while among the undiagnosed participants the scores did not present significant differences. Although the sample was very small, the need for cut-off points or differential criteria between men and women was emphasized.

All this leads us to the conclusion, as pointed out by Lai et al. [13], that current diagnostic methods (i.e. perhaps excessively dependent on ADOS and ADI-R) may showed low detection sensitivity of the behavioral ASD phenotype female; therefore, complementary measures had been pursued to improve sensitivity in the diagnosis of female ASD.

Kumazaki et al. [64] applied the CARS to examine gender differences comparing 20 girls and 20 boys aged 5-9 years, diagnosed with ASD/HF. They observed that boys scored significantly higher on "body use", "use of objects" or "activity level", while girls scored higher on aspects of sensory sensitivity (taste, smell and touch). If this differentiation is confirmed, this instrument could be an eligible candidate for complementing girl's early diagnosis.

Duvekot et al. [65] applied SRS-2-child as an ASD screening tool in general mental health centers for children and adolescents. They observed that the male-female ratio among the subjects diagnosed was 2.6:1, while with a later confirmed diagnosis the ratio varied significantly 3.7:1. These ratios suggest that women with difficulties in SRS screening tool are less likely to meet the diagnostic criteria for ASD even following rigorous standards of good practice. In this sense, is possible that there could be a nosological problem underlying the current ASD concept that would not contemplate the group of female autism manifestations.

Ratto et al. [66] also developed a multicenter study; out of a total of 816 participants (125 women) who did not have ID and met the diagnostic criteria for ASD by ADI-R, ADO or both. Participants were selected by age and IQ and using a random procedure to obtain two equal samples, finally constituting two groups (114 men and 114 women) in which the scores in both diagnostic instruments did not show significant differences according to sex. In their study, the authors introduced two complementary measures (i.e. SRS Vineland-II). The differences found according to the scales used should be achieved in the scales nature. In this sense, it is worth noting that the SRS is completed by parents or primary caregivers using a Likert scale and, unlike ADOS and ADI-R, and is standardized on the basis of sex, as the authors identified critical sex differences during the validation of this questionnaire. The scores are generated from the assessment of the five domains of the ASD traits (social awareness, social cognition, social motivation, social communication, and restricted/repetitive behaviors), indicating higher scores, higher levels in autistic traits divided by sex. On the other hand, the Vineland II is a scale that evaluates adaptive skills in individuals from 0 to 90 years, dividing adaptive behavior into three domains; communication skills, daily living skills and social skills. Since both SRS and Vineland-II are measures standardised by sex, it is indicating a pattern and showing that that autistic women were rated on this diagnosis tool (i.e. that relative compared them to typically developing women and not with men samples) as having more severe symptoms than autistic men when compared to typically developing men. As a result of this study and confirmed by others [63, 67], it can be concluded that any diagnosis that is excessively dependent on the scores of ADOS-2 or ADI-R could be clearly generating gender bias consequences.

In a recent multicenter study [68], a total of 8,982 cases (1,463 women) were collected, consisting possibly in one of the largest sample of women evaluated to detect ASD symptoms to date. Information from ADI-R, ADOS and SRS was available, and a parametric integrative random mixed-effect analysis model was constructed in which the sample was balanced by age, IQ and language level. The results do not demonstrate the existence of significant differences in severity levels evaluated by these tools, so the authors recommended as future lines of research to focus on possible false negatives, especially in women, which are those that are generally diagnosed later. This approach requires a complex, high-cost case follow-up studies. In addition, there is growing evidence that the diversity of both gender identity and sexual orientation is not only present in autism but, in fact, occurs in higher rates among autistic people [69].

We believe that one of the problems we face is precisely the lack of definition of an explicit behavioral phenotype of ASD in general (level of cognitive functioning, linguistic ability, learning ability, etc.) and, in particular, of the female phenotype and its evolution throughout personal development [70]. It is worth noting that there is an additional group of characteristics or additional behaviors to the (i.e. in relation to the symptomatological core described in DSM 5 or ICD 11) that we think that should be taken into account when discriminating the disorder presence in women and, even when they can't confirm the diagnosis, it could be desirable to determine a protocol to be followed in order to rule out false negatives in ASD women diagnosis. In this sense, the reviewed results on the use of standard tools such as ADOS and ADI-R are still unclear, and they need complementary information provided by tools (i.e. such as SRS and or Vineland-II) that can possibly improve the sensitivity to detect ASD in women too.

3. Other theoretical approaches

In order to answer the main research question of the present work, we have come across a body of information that, in many ways, is not conclusive and even reveals contradictory aspects. Therefore, and due to deepen the theoretical review, in this section we will focus on reviewing the existent evidence and the conceptual theories that would allow us to envision a more systematic and coherent theoretical alternative.

Is it worth mentioning the study conducted by Lockwood-Estrin and collaborators [71], which had as main objective to carry out a systematic study to determine the possible intrinsic difficulties that could be on the base of the existing biases in women ASD diagnosis (i.e. in girls and young women under 21 years of age). They identified two main groups of possible difficulties. First, that the group of symptoms and behaviors used for diagnosis (e.g. RRIB and CSID) are highly masculinized. Second, that there are other barriers to diagnosis such as a bias in evaluators or observers when considering, by training or deformation, that ASD are male disorders.

Regarding the first groups of difficulties, and regarding RRIB symptoms, it is worth mentioning that while in some cases a greater weight is attributed to repetitive behavior patterns and restricted interests in males [9, 72, 73, 74, 75, 76, 77]. These contradictions may be due to the so-called camouflage skills, most frequently developed by women [46, 27]; this skill is developed by learning and there is no evidence that it exists in young girls compared to evidence that it is detected in youth and maturity [78, 42]. A second justification in the underestimation of RRIB in women can be found in the biases of the evaluator, so that certain behaviors or restrictive interests of women, such as the interest for celebrities or self-image, cosmetics, etc., are perceived as more normal than other restricted male behaviors or interests [73, 79, 12, 43], while before the age of six there are no differences [29].

Regarding the CSID group of symptoms, some studies indicate that girls score higher in social skills than boys [72, 80], while others show an opposite pattern [61] and another group of studies completely denies any gender difference [73, 74, 12, 29, 80, 13]. Additionally, recent studies indicate the existence of a gender-differentiated profile in aspects related to oral expression [81, 82, 83].

Because of what was mentioned above, and as a consequence of the continuing contradictions found in the literature about the possible differences in gender in ASD, some other promising research lines have been proposed beyond the symptoms used for their diagnosis. In this regard, four main theoretical approaches can be distinguished in the literature: (a) the approach of brain differentiation; (b) the theory of the extreme male brain; (c) the theory of sexual differentiation Empathy-Systematization, and (d) the approach based on the use of complementary evaluation questionnaires. Next, we will explain each one of them, considering them a possible theoretical contribution that can constitute the basis for a possible effective tool of differential diagnosis by gender in ASD.

Regarding the theoretical approach based on brain differentiation, it was proposed that cognitive differences between men and women could explain why men were more likely to suffer from ASD. Although there are evident differences in the manifestation of ASD according to sex, which would probably indicate the existence of a female neuropsychological profile of autism, and there is no agreement on what characteristics would make up this ASD profile [29] and because if that it is necessary to develop differential tools to detect the specific symptoms in men and women or, at least, differential scales using sufficiently large and representative samples of both sexes.

The theory of the extreme male brain [84] postulates that autistic people would score, on average, towards more "male" positions [85]. The test so-called "Reading the Mind in the Eyes" is an instrument [86] derived from this approach which has been widely used to measure theory of mind (ToM) or the ability to recognize the thoughts and feelings of others; this test was applied in adults with autism (395 adults with autism, 178 men and 217 women, and 320 control adults, 152 men and 168 women), finding that, although some parts of the test reflected social difficulties that happened to be common to both sexes, the differences found between the groups fitted the extreme male brain postulate. In addition, the performance of women with autism differed more from that of same-sex controls than that of men with autism, and their self-assessment of symptoms was more consistent with test results than other groups.

The theory of sexual differentiation grounded on Empathy-Systematization (E-S) abilities [87] postulates that, in general population, people can be classified based on their score in these two dimensions. In this sense, empathy is understood as the impulse to recognize another person's state of mind and respond with an appropriate emotion. Systematization is defined as the impulse that a person can show to analyze and build a system that follows rules or patterns. A recent study [87] that was done on a sample of more than 670,000 participants, including more than 36,000 subjects with autism, attempted to demonstrate the theory of sexual differentiation E-S finding that male patterns tended to score high on the D scale (Difference between systematization and empathy); a high D score was related with men characteristic while a low D score was typically obtained in women. It is necessary to point out that empathy has two main forms or components, cognitive (ability to recognize another person's thought or emotional state) and affective (emotional response appropriate to the other person's feelings). Autistic subjects would score lower in cognitive empathy, by showing a deficit in mind theory but not necessarily in affective empathy. Additionally, women with ASD would score higher than average men on interpreting themselves to be generally hypermasculine, although they do not manifest other masculine traits such as aggressiveness.

Finally, there is a theoretical line that proposes the use of complementary evaluation questionnaires for evaluating main symptoms of ASD related constructs. For example, the Friendship Questionnaire (FQ) was used in a sample of 68 adults (51 men and 17 women) with ASD [88] showing that the two sub-samples (male and female) scored significantly lower than healthy controls but also that friendship relationship styles differed in the two sexes and additionally supporting the theory of the extreme male brain.

To sum up, we believe that these four general explanatory approaches could be useful in finding a possible diagnostic plot line that would allow generating appropriate theoretical bases to create an effective tool for differential diagnosis of ASD by sex.

4. Discussion and conclusions

The theoretical review carried out in this article showed that in recent years there has been an increase interest in the female phenotype of ASD characterization. We think that the reason for this interest lies, on the one hand, in determining whether there is any protective factor that could be identified and, secondly, whether the problem lies in the diagnostic instruments or in the use of them. As it was argued on the present work, to date, the studies consulted clearly provide inconclusive results.

We think that is worth mentioning that it is important to distinguish between sex and gender in the context of autism. Sex is a biological or physiological characteristic while gender is a socio-cultural construct [89] but gender could be defined as the combination of biological sexual characteristics with factors related to behavior, social roles, lifestyle, life experiences, etc. [90].

In addition to the possible bias introduced by clinicians and researchers, the most widely used instruments for the diagnosis of ASD (ADI-R and ADOS) also present a certain bias when assessing the traits in women. They were built on the nosological concept that ASD were male disorders and, therefore, questions and situations that are presented to the participant, tend to evaluate more male conditions. In addition, the scale to determine the cut-off points of each instrument has been also performed on gender-biased samples. All this leads us to think that, regardless of the possible female phenotype of ASD, it is necessary to investigate more and even develop analytical tools or complementary instruments for a proper diagnosis in women. The evaluation instruments review a done and exposed on the present article, allows us to conclude that women with autism, and especially those with high functioning (HFASD), are in a very vulnerable situation as they go unnoticed and cannot access the services and resources they need. In addition, they normally are not exempt from stereotypes, gender roles and social expectations (being affectionate, pleasant, friendly, sociable, etc.) which adds an additional stress burden to apart from all that was mention above. As a result, these women may feel misunderstood, with greater social pressure to be normal and with more internalizing problems (i.e. especially anxiety and depression), and with fewer opportunities to access health services, educational and social that would help them improve their quality of life [90].

Additionally, the common comorbidity of mental disorders in women with HFASD poses a double problem. On the one hand, by failing to detect and diagnose HFASD, they are considered to show a neurotypical development and are normally removed from early intervention programs. On the other hand, they are normally diagnosed with another disorder, or they develop it as a consequence of the sustained stress and anxiety that they suffer.

Based on the theoretical review carried out, two possible lines of research are proposed for future research. Regarding diagnostic tools, we think that they should be improved by including not only all the criteria established in DSM 5, but also other variables that recent studies have shown to be present HFASD subjects, such as socialization styles, friendship relationships, the pattern of look and avoidance of it, the analysis of the type of speech, etc. On the other hand, and regarding the approaches that we have reviewed to arrive at a possible theoretical explanation of the lower prevalence of HFASD diagnosis in women we found that, together, they can be valued as the basis for a possible effective gender differential diagnostic tool in HFASD and they could be proposed to find a possible diagnostic plot line that would allow future research to generate appropriate theoretical bases to create an effective HFASD gender differential diagnostic tool. For it, we consider that another diagnostic tools research line could be that which evaluates, by means of properly validated and assessed questionnaires, aspects of female HFASD (i.e. different from that described by possible extreme male brain) and based mainly on more specific aspects of the female gender such as those studied in the Empathy-Systematization approach and including the measurement of possible intervening co-variables such as those described in the section on the use of complementary evaluation questionnaires.

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