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Gender medicine and paediatrics: present and future perspectives

Isabella Tarissi De Jacobis[1], Francesca de Gennaro[2], Giulia Ceglie[2], Alberto Villani[1]

1. University Hospital Paediatric Department, General Paediatrics and Infectious Diseases, Bambino Gesù Hospital Rome, Italy;
2. University Hospital Paediatric Department, Bambino Gesù Hospital, Università di Roma Tor Vergata, Rome, Italy.
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Summary. In paediatric literature, there are data, although limited, which indicate the presence of specificity in the two genders. In this work, we have reviewed the literature data regarding gender differences specific to some paediatric pathologies, comparing these data with those collected by Ospedale Pediatrico Bambino Gesù of Rome. For many infectious diseases, the incidence is greater in men; women develop both a greater and longer lasting humoral and cell-mediated immunity response which protects from infections but exposes one to a greater risk of developing auto-immune and inflammatory pathologies. For many vaccines, a greater antibody response has been demonstrated in women. However women develop adverse effects more often and with greater intensity. The majority of auto-immune diseases show a gender-specific preponderance, in particular women show a significantly greater risk to develop these pathologies; the incidence in the two genders is more evident in adults, but it is also observed in paediatric age groups. The gender differences concern not only the response to infections, vaccines or immune dysregulation, but it may also involve other fields of medicine such as neuropsychiatry and orthopaedics.

Key words: differences, gender, paediatrics.

Medicina di genere e pediatria: presente e prospettive future

Riassunto. In Pediatria vi sono in letteratura dati, seppur ancora limitati, che indicano la presenza di specificità nei due sessi. In questo lavoro abbiamo rivisto i dati della letteratura sulle differenze di genere in pediatria in alcune patologie, comparando anche questi dati con quelli ricavati dalla casistica dell'Ospedale Pediatrico Bambino Gesù di Roma. Per molte malattie infettive l'incidenza è maggiore nei maschi; nelle femmine si sviluppa una risposta immunitaria sia umorale sia cellulo-mediata superiore e prolungata che risulta protettiva verso le infezioni, ma che espone a un maggior rischio di sviluppo di patologie autoimmuni e infiammatorie. Per molti vaccini è stata dimostrata una risposta anticorpale maggiore nelle femmine. Le femmine tuttavia presentano più spesso e con maggiore intensità gli effetti avversi. La maggior parte delle malattie autoimmuni presenta una preponderanza sesso-specifica: in particolare, le donne presentano un rischio notevolmente maggiore di sviluppare queste patologie, la differenza d'incidenza nei due sessi è più evidente negli adulti ma si riscontra anche in età pediatrica. Le differenze di genere non riguardano soltanto la risposta alle infezioni, ai vaccini o alla disregolazione immunitaria, ma possono interessare anche altri ambiti della medicina come la neuropsichiatria e l'ortopedia.

Parole chiave: differenze, genere, pediatria.

Introduction

Gender medicine or Gender-specific medicine is an innovation in health treatment science. In Italy, a stronger focus on sex and gender differences, both in diagnoses and treatments, started to develop in 1998 and is substantially more visible in recent years. Sex and/or gender differences in adults have been documented in the literature with regard to various pathologies, both in terms of incidence and prevalence, as well as the clinical course and complications.

These differences are the results of hormonal, genetic, epigenetic and socio-environmental factors (nutrition, work environment, smoking, alcohol, sports, etc.) which are different in the two genders. In paediatrics literature, there are data, although limited, which indicate the presence of specificity in the two genders. Statistics and numbers do not explain yet if the cause of this diversity lays in genetic, metabolic, hormonal, environmental or in other factors.

Already in the foetus, the gender, male or female, affects the possibility of developing different anomalies, including premature births or c-section delivery.

In this work, we have reviewed literature data regarding gender differences specific to some paediatric pathologies, comparing these data with those collected by Ospedale Pediatrico Bambino Gesù of Rome. The areas that we will be addressing concern, in particular, infections, immunity, vaccine response, auto-immune diseases, neuropsychiatry and orthopaedics.

Infections, immunity, vaccine response

For many infectious diseases, the incidence is higher in the male gender[1-2]. The main reason for this difference seems to be the development in women of an

immune response, both humoral and cell-mediated, which protects from infections but exposes them to a greater risk of developing auto-immune and inflammatory pathologies. For this reason, viral infections are more frequent in men, however the course of the disease seems to be worse for women as a result of their greater immune-reactivity and their risk for immunopathogenic risk[3-4].

Within the areas of several types of infections, we find differences, for example, bacterial infections of the lower airways are more frequent and severe in men, while those of the upper airways are more frequent and severe in women[2-3]; sepsis and bacterial meningitis are more frequent in men, especially in the first month of life[1].

The different susceptibility between the two genders seems to be attributable to a number of differences involving both the immune and hormonal but also the genetic systems:

- *Genetic differences:* many genes related to the immune system are found on the X chromosome[1-4].
- *Differences in the innate immunity:* women show a greater expression of the Toll-like receptors and a greater phagocyte activity of macrophages, neutrophils and cells that present the antigen[4].
- *Differences in the acquired immunity:* the antibody levels, the cytokine responses and the counts of CD3 and CD4 are greater in women[4].
- *Hormonal differences:* low-dose estrogens stimulate the Th1 (Th, T helper) response, while greater doses stimulate Th2 and antibody production; testosterone plays an immune-suppressive role[4-5].

Following are some examples of infectious pathologies with a relevant incidence in paediatric age and of which some gender differences are known.

Bronchiolitis. Bronchiolitis is the infection of the lower airways. It is more common in children under 2 years of age and one of the main causes for hospitalisation of children between the ages of 3 and 6 months. Although the Respiratory Syncytial Virus is the most common cause, other viruses may be associated with it (Rhinovirus, Bocavirus). The existing literature shows that their incidence is greater in males[3,6-8]. Some studies have demonstrated that the male gender represents a greater risk for the severity of the disease, with a more frequent hospitalisation and oxygen based treatments[7-12]; others suggest that in male and female infants under the age of 6 month fever episodes are more frequent, while laboratory altered values (increase in C-reactive protein and leukocytosis) are more frequent in female infants, except for the evidence of eosinophilia[13]. Furthermore, studies on the long term outcomes show that a history of bronchiolitis is a risk factor in the development of asthma in males and how males with a history of bronchiolitis show a greater bronchial hyperactivity[14-16]. Through a retrospective study, currently under way, conducted on healthy patients admitted to the Ospedale Pediatrico Bambino Gesù for bronchiolitis, we have observed how the use of oxygen and steroids was much greater in male rather than female newborns. In the case of infants, the same has shown to be more common in females. A prolonged hospitalisation (>5 days) seems to be greater in female patients, both with newborns and infants. C-protein reactive alteration and thrombocytosis seem to be slightly greater in females rather than males. However, within the infant group, these alterations seem to be more common in males. Therefore, these preliminary data seem to be partially consistent with the literature data. Different data could be due to the limited number of patients who were examined to date and to the different treatment approaches adopted by the hospital care units.

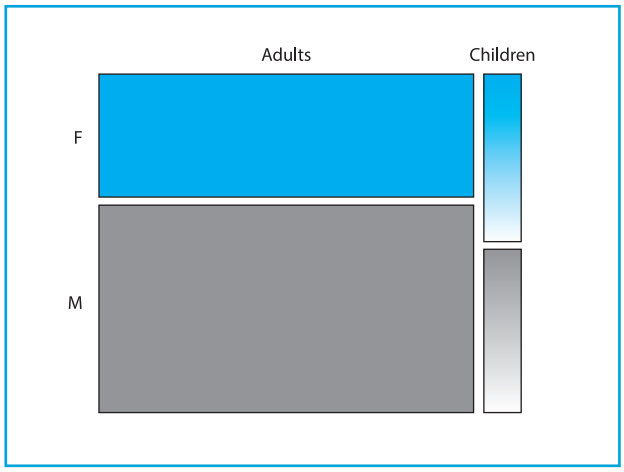

Figure 1. Global incidence of tuberculosis broken down by age and gender.

Tuberculosis. To date, tuberculosis represents a more significant problem worldwide. According to the Global Tuberculosis Report from the World Health Organization of 2015, 10.4 million new tuberculosis cases have been estimated, of which 5.9 million were among adult men and 3.5 million among adult women (M:F ratio 1.6:1), 1 million (10%) among children (Figure 1).

In 2015, 6.4 million new cases in male patients (0.47 million children) and 4 million new cases in female patients (0.48 million children) were estimated worldwide. The M:F ratio of the new tuberculosis cases for all ages ranges between 1:1 in the Eastern Mediterranean regions and 2:0 in the Western Pacific regions. A similar M:F ratio was estimated for adults, while in children the M:F ratio ranges from 0.9 in the Eastern Mediterranean regions to 1.1 in the Western Pacific regions.

Table 1. Estimated incidence of tuberculosis by age and sex in 2015.

	0-14 years	>14 years	Total
Females	12 (10-14)	99 (84-116)	111 (94-130)
Males	13 (11-14)	199 (181-219)	212 (192-233)
Total	25 (22-27)	299 (285-312)	323 (299-349)

Table 2. Yearly incidence of osteomyelitis by age and gender in the Olmsted county (1969-2009).

Age (years)	Number of cases			Incidence rate (every 100,000 persons/year)		
	Females	Males	Total	Females	Males	Total
<18	41	71	112	6.6	10.9	8.8
18-29	22	42	64	5	10.9	7.8
30-39	20	46	66	5.7	13.2	9.4
40-49	20	40	60	6.8	14	10.4
50-59	46	71	117	20.8	33.5	27
60-69	52	67	119	33.4	49.2	40.8
70-79	57	54	111	49.4	66.7	56.5
80	61	50	111	70.3	128.4	88.3
Total	319	441	760	16.7	27.7	21.8

Modified from Kremers et al., 2015.

The global M:F ratio, based on the reports, is 1.7. The differences among the various countries in the M:F ratio could reflect the actual difference in epidemiology but can also be related to the different possibility of access to the services of public health and to different reporting practices.

As for Europe, estimated data show 12,000 new cases in females <14 years of age and 13,000 new case in males < 14 years of age (M:F ratio 1.08:1)[17] (Table 1).

As regards the paediatric cases in our hospital (Ospedale Pediatrico Bambino Gesù) of new cases of pulmonary and medianistic tuberculosis reported between 2000-2016, 144 new cases were reported for females (49%) and 150 new cases for males (51%) with a M:F ratio equal to 1.04:1 ratio, almost overlappable to the one reported by the World Health Organization.

Osteomyelitis. Osteomyelitis is a localised infection in the bone, in the paediatric age, the most frequent form of which is the haematogenous acute osteomyelitis. Also for this pathology, the literature reports an important difference in the incidence between genders for all ages, including children, with a net prevalence in males[18-20] (Table 2).

The cases treated in Ospedale Pediatrico Bambino Gesù were 97 patients hospitalised for osteomyelitis from 2010 to 2016, of which 63 males and 34 females (M:F ratio 1.85:1).

Meningitis. Meningitis, despite the availability of powerful antimicrobials, continues to be one among the ten most frequent causes of mortality and morbidity in children. Both the viral and bacterial meningitis (for all the main involved pathogens) seem to be more prevalent in males, although with a different M:F ratio[21-24]. Our data (Ospedale Pediatrico Bambino Gesù) on cases of meningococcal meningitis (confirmed by laboratory tests) show 32 cases between 2006 and 2015, with 47% of cases in females and 53% in males, thus confirming the differences in gender highlighted in the literature.

Vaccines. The differences at the basis of the different susceptibility and response to infections play a very important role also in the different vaccine responses in the two genders. For many vaccines (hepatitis A and B, flu, yellow fever, measles, tetanus, diphtheria, smallpox,

anti-pneumococcal diseases), an antibody response was greater in females who, however, show more frequently and with greater severity adverse events[4,25-29]. The difference in the vaccine response between the two genders is present in each age range[27], however in menopause the capacity to build an adequate antibody response is reduced, although the hormone replacement therapy shows beneficial effects on the immune system (increase in lymphocytes B, reduction in pro-inflammatory cytokines)[25]. The differences in terms of vaccine response is therefore found in both the adult and the paediatric populations. Following are some examples of adult population, taken from the literature:

- Women who have been vaccinated against flu with half dose vaccine show the same antibody response of men vaccinated with the full dose[4;25-26;29-30].
- Women and men with the lowest levels of androgens develop a greater antibody and cytochinic response to the trivalent inactivated flu vaccine[31].
- In the smallpox vaccine, the gender is strongly related to the development of neutralising antibodies, in fact women show a greater response than men[32].
- The antibody response to IMVAMUNE (a vaccine against smallpox which is highly attenuated as a safe option to the live virus vaccine) seems to be greater in men than women[33].
- Women vaccinated with two antitetanus doses show a better response than men[34].
- In older men, a specific antibody concentration seems to be greater both before and after the anti-pneumococcal vaccination (23-valent); this evidence may be due to the habit of smoking, which is more frequent in men and is a factor of risk for respiratory infections[35-36].

In the paediatric population, many authors have demonstrated that young girls develop a greater antibody response to the measles-mumps-rubella vaccine, to the anti-measles vaccination with Edmonston-Zagreb vaccine, to the meningococcus vaccine for the strains A, W and Y, and to the diphtheria vaccine[26;37-40]. Voysey et al. have also highlighted that the antibody persistence after the pneumococcal vaccination (10-13 valent) is greater in women[38].

As already mentioned earlier, Klein et al. have shown that adverse effects, after the measles-mumps-rubella vaccination, develop more frequently in women, except for the Autoimmune thrombosis purpura[37]. Finally, according to Voysey et al. there seem to be no differences between males and females in the response to vaccination against the tetanus and the haemophilus influenzae type B[38].

In the period between 1 January 2017 and 30 April 2017, 47 patients (22 males) between the ages of 8 days - 17 years (average age 3.25 ± 1.12) with a measles diagnosis, were hospitalised at the General Paediatric and Infectious Diseases Operating Unit of Ospedale Pediatrico Bambino Gesù of Rome. The diagnoses were clinically based and confirmed by the presence of specific immunoglobulins M specific of measles on the serum, or with a molecule-based diagnosis through the evidence of the virus found in the blood and/or urine through a PCR (polymerase chain reaction).

The vaccine status was classified as: complete (2 doses), partial (1 dose), not vaccinated by parental choice and not vaccinated because of an age below the recommended one in the national vaccination plan.

Of the 47 patients: 18 (38.2%) were not vaccinated by choice; 25 (53.19%) had not reached the minimum age required for vaccination; 4 patients, all of them males (8.5%), had requested only one dose of the measles-mumps-rubella vaccine.

This data, although limited, would confirm what is reported in the literature about the immune response to the measles-mumps-rubella vaccination in the male gender.

Autoimmune diseases

The majority of autoimmune diseases show a gender-specific preponderance; women, in particular, have demonstrated a significantly greater risk than men to develop these pathologies. The incidence peak of autoimmune diseases is between the age of 40 and 50, however many of these pathologies may be developed also during childhood and adolescence. The difference in incidence between the two genders is more evident in adults but it is also observed in paediatric age[41].

In adults, the difference in incidence may be explained for the most part by the hormonal differences between the two sexes, even if the exact mechanism on which this difference is based is not totally known. Among the factors involved, there exist genetic, environmental but especially hormonal differences. It is in fact known that the levels of androgens and estrogens differ in the period when the incidence peak of the autoimmune diseases is observed, and their role in regulating the immune response is broadly recognised[42].

However, in the cases of their development before puberty, these hormonal differences may explain only marginally the diversity of incidence between males and females and it can therefore be assumed that there are other mechanisms at the basis of these differences in paediatric age. It is in fact demonstrated that from the ages of 6 months to 7 years the levels of estrogens and estradiols are very low both in little boys and girls[43]. Among the mechanisms involved, an important role is probably to be attributed to genetic differences.

For example, some genes in the non-recombinant Y chromosome region could play an important role in

regulating the immune response[44]. In support of this hypothesis is the evidence that among the subjects with Klinefelter syndrome (47, XXY)[45], females have an increased risk of auto-immune diseases while among the subjects with the Turner syndrome (45, X), males have a greater risk of developing these pathologies[46].

Systemic lupus erythematosus. Among autoimmune diseases with a different incidence in the two genders, the systemic lupus erythematosus incidence is different in paediatric versus adult age. In fact, in adults the ratio is significantly more relevant in favour of the females (M:F = 1:9) while in children this difference is less significant based on a M:F ratio of approximately 3:4[47-48]. The systemic lupus erythematosus developed in paediatric age is different than when developed by adults since it is, in the latter case, more severe and characterised by a greater risk in renal, haematological and neurological effects (in particular psychosis, chorea, encephalopathy, whereas the involvement of cranial nerves is more frequent in adults)[47-49]. In addition, children show more frequently anti-DNA and anti-cardiolipin antibodies and the use of steroids is greater the earlier the onset of the disease is[48]. As regards gender differences, the male gender is a risk factor for sub-clinical diseases of the coronary arteries[48]. In general, it seems that the onset in childhood age is associated with an increased number of susceptibility alleles[48]. In addition, the role of the micro RNAs (miR) in the different expressions of lupus-associated genes is emerging in the literature. The micro RNSs are RNA single-stranded non-coding molecules which regulate the post-transcriptional gene expression and their role was highlighted in terms of regulating the cellular differentiation in the development of the immuno tolerance and in the involvement in the pathogenesis of different pathologies[50]. For instance, the miR-181-a: expressed in the haematopoietic cell line, modulator of the maturity, function and differentiation of the T and B lymphocytes is significantly down-regulated in paediatric patients with systemic lupus erythematosus[50], while the miR-146-a seems to regulate negatively the production of interferon α (higher serum level in paediatric patients with α systemic lupus erythematosus and especially in those with an active disease and the innate immune response, acting on the kinase associated with the interleukin1 receptor (IRAK1) and with the factor 6 associated with the receptor for the Tumor Necrosis Factor (TRAF6); under-expressed in patients with systemic lupus erythematosus, with a more reduced expression in patients with the active disease[51].

Juvenile idiopathic disease. The gender differences are found also in other rheumatological diseases such as juvenile idiopathic disease in which the distribution by gender seems to be equal except for the systemic onset form[52] and oligoarthritis[53] which are more prevalent in the female gender. Some studies, carried out on children in Western countries, report an increased prevalence of juvenile idiopathic disease in the female population, while other studies, carried out on children in Eastern countries, show a slight male prevalence. This difference in the incidence and expression of a disease may be linked to a different immunogenetic background among the different ethnic groups[54]. In addition, antinucleus positive antibodies are found more frequently in females and the females seem to develop more easily radiological alterations that suggest an important articular involvement (erosion, reduction in the articular space, ankylosis, subluxation).

Type 1 diabetes mellitus. Another autoimmune pathology with an onset found in more than half the cases in paediatric age is the type 1 diabetes mellitus. In fact, the onset age has two peaks, the first between the age of 5 and 7 and the second during puberty. Between the ages of 5 and 7, the ratio is F:M= 1:1.1, while in puberty the ratio is 1:1.7. In the adult age the ratio is F:M=1:1.5[51,53-55]. Different proteins have been identified as possibly responsible for the genetic susceptibility to the autoimmune pathologies, in particular those involved in the interactions with the lymphocytes T. Among those, the role of the HLA (human leukocyte antigen) is known to confer susceptibility to the development of type I diabetes and other autoimmune pathologies. Another locus that was recently identified as a possible susceptibility factor, is the PTPN22 (*protein tyrosine phosphatase N22*) gene which is found in the 1p13 chromosome and encodes a lymphocyte-specific alkaline phosphatase expressed in both the T and B lymphocytes acting as an inhibitor of the pathway of antigen-specific activation of the T lymphocytes[56]. However, in the PTPN22 gene, the 1858T allele seems to be associated with the type 1 diabetes pathogenesis in females[57]. This association has been found only in the type 1 diabetes and not in other studied autoimmune pathologies (Hashimoto's thyroiditis, Addison disease)[58]. The sex hormones represent probably the main mediators of these differences in the two genders through the steroid receptors which operate as transcription factors and play a role in the expression of susceptibility genes such as PTPN22[58].

Important gender differences are also observed among the most frequent gastrointestinal auto-immune-based pathologies.

Coeliac disease. The coeliac disease has a predominance in the female gender[59-61], in fact women seem to have a greater risk of developing it[62-65]. In addition to the incidence, the gender seems to have an impact also in the manifestations and severity of the pathology. In fact, in

women over 14 years old, a lower percentage of silent pathology and iron deficient anaemia seems to prevail, whereas adult males seem to have a greater risk of malnutrition with lower serum cholesterol levels and lower bone density[59]. At a laboratory test level, the female population shows greater levels of auto-antibodies[62] and females seem to show more frequently encoding alleles for DQ2 or DQ8; in fact the presence of these two molecules seems to be a stronger risk factor in females[66] while the males seem to develop this pathology more frequently in the absence of the HLA predisposition[66]. On the other hand, the male gender seems to be a risk factor for the development of T cell lymphoma[67]. There are different theories to explain these differences. There are different effects resulting from the maternal and paternal DQ2 haplotypes in males and females and this is probably due to the HLA region imprinting phenomenon with gender-specific differences in terms of gene susceptibility. The data showing that females are more frequently the carrier of a paternal DQ2 haplotype substantiates this hypothesis[66].

Crohn's disease. On the other hand, the Crohn's disease has a greater incidence in males in their childhood, in particular under the age of 10, whereas the pathology is preponderant in female adults[68-69]. However, the disease is more severe in females with a greater prevalence of extra-intestinal manifestations, of hypoalbuminemia at diagnosis and increased need for surgical treatment[68-70]. Females show more frequently, as an early symptom, mouth sores, rectal bleeding and joint pain[69] and need more often a cyclosporin-based treatment[69]. The theories that explain the greater incidence of the Crohn's disease in males of the paediatric population are different. For example, some genes increase susceptibility to the disease in males or play a protective role in females. Among them, there is a single nucleotide polymorphism in the interleukin-6 promoter which determines a limited transcription of the interleukin-6. This cytokine plays an important role for the differentiation of the Th17, the promoter is negatively regulated by estrogens and the males without polymorphism have an earlier onset age, while in the females polymorphism-related differences in the onset age are not observed[71]. On the other hand, the DLG5 gene encodes a granulate cyclase membrane involved in the exchange of extra-cellular signals with the cytoskeleton, and while maintaining an intestinal integrity, it works on the intestinal permeability; it seems to be a target gene of the progesterone. Its R30Q variant has a protective effect on susceptibility in females of paediatric age[72-73] (probably it loses its protective capacity following the puberty hormonal changes) while it confers an increased risk in males[72].

Gender differences in other pathologies: some examples

The gender differences concern not only the response to infections, vaccines or immune dysregulation, but they also involve other areas of medicine such as neuropsychiatry and orthopaedics.

Some examples may be represented by autism, Attention Deficit Disorder/Hyperactivity and Nervous Anorexia, and in the orthopaedic area, juvenile idiopathic scoliosis.

Autistic disorders. The prevalence of the spectrum of autistic disorders is greater in males, with an average M/F ratio of 4:1[74-77]. To date, the causes of this male preponderance are still unknown but there are different hypotheses to this regard:

- The males are more vulnerable to a number of prenatal insults (infections, malnutrition, etc) and are more susceptible to relevant genetic mutations in the autism[77].
- Females are more resistant to potential deleterious pre-natal factors and need a greater "genetic load" to become symptomatic[75-77].

However the diagnosis of disorders within the autistic spectrum in females is associated with a greater severity of the pathology and a lower intellectual quotient (probably because of the greater mutational load required for the expression of the pathology)[77].

Some co-morbidities within the autistic spectrum disorders seem to also show gender differences[78]:

- The Attention Deficit Disorder/Hyperactivity seems to be more frequent in males
- Epilepsy seems to be more frequent in females

There are no specific causes that explain these particular differences.

Attention Deficit Disorder/Hyperactivity (ADHD). The Attention Deficit Disorder/Hyperactivity is one of the most common neuropsychiatric disorders with childhood onset, the prevalence of which increases with age. This disorder seems to be more frequent in males with a different M:F ratio based on the sub-type. A decisive male predominance is found in the sub-type with hyperactivity (M:F ratio 4:1), less strong is, on the other hand, the difference in the attention deficit disorder sub-type (M:F ratio 2:1)[79]. According to a review by Williamson et al., concerning the adult population, the difference in prevalence between males or females tends to be lower with age. In fact some cited studies report a greater prevalence of the Attention Deficit Disorder/Hyperactivity in women. One of the possible explanations could be related to the gender difference in the

subtypes of the Attention Deficit Disorders/Hyperactivity; it seems in fact that the hyperactivity symptoms, more frequent in males, tend to improve with age as opposed to the attention deficit which affects mostly the female gender. Also in this neuropsychiatric disorder, there seems to be a gender difference in the possible co-morbidity, with more women predisposed to develop pathologies such as depression and bulimia and more men affected by antisocial disorder and abusive behaviour. Not all studies agree on the above[80].

Eating disorders. Eating disorders are more frequent in women, although recently some interesting data have emerged concerning the prevalence of these disorders in the male population. In particular in recent months, the number of diagnoses of eating disorders in males has increased. Whether the nature of this increase is associated with a real increase of male cases, or if there is simply a greater awareness of the possibility of this disorder also in boys, is still being debated. Hudson et al.[81] have estimated that the prevalence of nervous anorexia in the male population is 0.3% and 0.5% for nervous bulimia. On the other hand, the binge eating disorder may affect up to 2% of the male population. Based on this data, 25% of the individuals with anorexia and nervous bulimia, and 36% of the cases of binge eating disorders (diagnosed according to DSM-IV criteria) are represented by males. Other studies, reported in the literature[82], state that the sub-clinical forms of eating disorder behaviour, such as occasional binge eating, the use of laxatives, prolonged fasting, are as frequent in males as in females. In addition, a greater mortality is reported in the male versus the female population[83] as well as a greater risk to develop co-morbidities such as depression, substance abuse and anxiety[84]. From the above data, it is evident that to consider eating disorders as an exclusively female issue is an error that may lead to underestimating this problem in the male population with a consequent increase in co-morbidity and mortality associated with these types of disorders.

Juvenile idiopathic scoliosis. As regards orthopaedic pathologies, the juvenile idiopathic scoliosis is a clear example of how gender differences also affect this area. The juvenile idiopathic scoliosis is characterised by a pathological curvature of the spine with an onset between the age of 10 and the skeleton's maturity and has an estimated 0.2-3% prevalence in the general population. Etiopathogenesis is not clear and the most reliable current hypothesis is a multi-factor pathogenic pattern where both genetic and environmental factors play a role; in addition it is more frequent in the female population and involves more frequently girls during puberty. The female: male ratio ranges from 2:1 for smaller curvatures and increases with the increase of the curvature up to 10:1 in the >30°[85]. The pathogenesis of this pathology seems to be based on multiple factors involving both genetic, epigenetic and hormonal factors. As regards genetics, some genes, involved in both autosomes (cr 6-10-17-18-19) and chromosomes X have been identified[86-87]. However, despite numerous studies, no single gene has been identified as being responsible for this pathology. In particular, among the factors involved in determining this gender difference, the estrogens play a fundamental role since they can affect the progression of the spine deformation. The estrogens, in fact, repress the production of the osteoclastogenic cytokines by increasing the osteoblastic proliferation and reduce the osteoblast apoptosis and cause the osteoclastic one. The result of these effects is pro-osteoclastogenic and counter-osteoclastic. The lack of estrogens could therefore lead to an increase in the bone turn-over[88].

The data from Ospedale Pediatrico Bambino Gesù in a study, aimed at investigating the ratio of juvenile idiopatic scoliosis and gender, have been collected by administering to 111 patients (17 males and 94 females) with severe juvenile idiopatic scoliosis (having undergone corrective treatment) a questionnaire aimed at highlighting the correlation between scoliosis and clinical-historical data (family history, physical activity, menarche, height). Preliminary data show that the incidence of the pathology is considerably higher in females (85% of the cohort). This data is consistent with the figure reported in the literature. The family history, in the case of scoliosis, is slightly greater in males (41% vs 35%). We have also noted that the current average height of affected females is, in 60% of the total number of patients, > 160 cm and the menarche, in 39% of the cases, occurs after the age of 12.5. As regards physical activity, the sport more frequently practised during childhood is swimming (35%) followed by dance for young girls (24%). The data collected on incidence confirm the literature data; however in order to draw definitive conclusions on other data is to date difficult given the small size of the studied sample.

Conclusions

In Paediatrics, a wide spectrum of pathologies develops in the two genders with a different incidence, prevalence and clinical characteristics. Statistics and numbers do not explain yet if the cause of this diversity lays in genetic, metabolic, hormonal, environmental or in other factors. From the reported data, it is clear that gender differences, and in particular gender-specific medicine, has become not only an interesting area of research but also a clinical necessity both for the adult

and paediatric age groups. The paediatric environment, in particular, was only marginally explored in this sense and this opens new and very stimulating future opportunities both in terms of research and clinical applications. The use of different pathways for prevention and diagnosis with targeted screenings which take into account differences in the incidence of the pathologies in the two genders, may allow for an early diagnosis of gender-specific pathologies with a consequent reduction in the severity of the pathology itself and its complications. A therapeutic approach that takes into account gender-specific diversities would lead to a more tailored management of the pathologies themselves with a reduction in the short and long term complications. In the area of vaccines, keeping into account the differences in the antibody response in the two genders may lead to better vaccine coverage, thus minimising adverse reactions.

All of this would have an important relevance, not only from a clinical perspective but also in terms of healthcare costs and expenditures.

Key messages

- For many infectious diseases, the incidence is higher in the male gender.
- For many viruses, a greater antibody response has been demonstrated in women.
- The majority of autoimmune diseases presents a specific gender preponderance.
- The gender differences refer also to fields of medicines such as neuropsychiatry and orthopaedia.
- The gender medicine objective is the development of customised diagnostic-therapeutic processes that keep into account the gender-specific clinical differences.

References

1. Washburn TC, Medearis DN Jr, Childs B. Sex differences in susceptibility to infections. Pediatrics 1965;35: 57-64.
2. Del Principe D, Marconi M, Matarrese P, Villani A, Malorni W. Gender disparity in pediatric diseases. Current Molecular Medicine 2013; 13(4): 499-513.
3. Muenchhoff M, Goulder PhJR Sex differences in pediatric infectious diseases. J Infect Dis 2014; 209(Suppl 3): S120–S126.
4. Ruggieri A, Anticoli S, D'Ambrosio A, Giordani L, Viora M. The influence of sex and gender on immunity, infection and vaccination, Ann Ist Sup Sanità 2016; 52(2): 198-204.
5. Reardon S. Sexes deal differently with infection, Nature 2016; 534: 447.
6. Hasegawa K, Tsugawa Y, Brown DFM, Mansbach JM, Camargo CA. Temporal trends in emergency department visits for bronchiolitis in United States, 2006-2010. Pediatr Infect Dis J 2014; 33(1): 11–18.
7. Semple MG, Taylor-Robinson DC, Lane S, Smyth RL. Household tobacco smoke and admission weight predict severe bronchiolitis in infants independent of deprivation: prospective cohort study. PLoS One 2011; 6(7): e22425.
8. Koehoorn M, Karr CJ, Demers PA, Lencar C, Tamburic L, Brauer M. Descriptive epidemiological features of bronchiolitis in a population-based cohort. Pediatrics 2008; 122(6): 1196-203.
9. Lanari M, Prinelli F, Adorni F, et al. Risk factor for bronchiolitis hospitalization during the first year of life in a multicenter italian birth cohort. Ital J Pediatr 2015; 41: 40.
10. Alvarez AE, Marson FA, Bertuzzo CS, Arns CW, Ribeiro JD. Epidemiological and genetic characteristics associated with the severity of acute viral bronchiolitis by respiratory syncytial virus. J Pediatr (Rio J) 2013; 89(6): 531-43.
11. Law BJ, Langley JM, Allen U, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. Pediatr Infect Dis J 2004; 23(9): 806-14.
12. Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. J Pediatr 2003; 143(5 Suppl): S118-26.
13. Nagayama Y, Tsubaki T, Nakayama S, et al. Gender analysis in acute bronchiolitis due to respiratory syncytial virus. Pediatr Allergy Immunol 2006; 17(1): 29-36.
14. Mikalsen IB, Halvorsen T, Øymar K. The outcome after severe bronchiolitis is related to gender and virus. Pediatr Allergy Immunol 2012; 23(4): 391-8.
15. Tse SM, Coull BA, Sordillo JE, Datta S, Gold DR. Gender and age specific risk factors for wheeze from birth through adolescence. Pediatr Pulmonol 2015; 50(10): 955-62.
16. Tse SM, Rifas-Shiman SL, Coull BA, Litonjua AA, Oken E, Gold DR. Sex specific risk factors for childhood wheeze and logitudinal phenotypes of wheeze. J Allergy Clin Immunol 2016; 138(6): 1561-1568.e6.
17. WHO. Global Tubercolosis Report 2016.
18. Funk SS, Copley LA. Acute hematogenous osteomyelitis in children: pathogenesis, diagnosis, and treatment. Orthop Clin North Am 2017; 48(2): 199-208.
19. Sreenivas T, Nataraj AR, Menon J, Patro DK. Acute multifocal hematogenous osteomyelitis in children. J Child Orthop 2011; 5(3):231-5.
20. Kremers HM, Nwojo ME, Ransom JE, Wood-Wentz CM, Melton LJ 3rd, Huddleston PM 3rd. Trends in epidemiol-

ogy of osteomyelitis – A population based study 1969 to 2009. J Bone Joint Surg Am 2015; 97(10):837-45.
21. Shrestha RG, Tandukar S, Ansari S, et al. Bacterial meningitis in children under 15 years of age in Nepal. BMC Pediatr 2015; 15: 94.
22. Hentgen V, Levy C, Bingen E, Cohen R; groupe des pédiatres et microbiologistes de l'Observatoire national des méningites bactériennes de l'enfant. Group A streptococcocal meningitis in children: clinical characteristics and outcomes. Arch Pediatr 2008;15 Suppl 3: S154-7.
23. Theodoridou MN, Vasilopoulou VA, Atsali EE, et al. Meningitis registry of hospitalized children: epidemiological patterns of acute bacterial meningitis throughout a 32-year period. BMC Infect Dis v.7; 2007.
24. Wan C. Viral meningitis: background, pathophysiology, etiology. Medscape, 2016.
25. Giefing-Kröll C, Berger P, Lepperdinger G, Grubeck-Loebenstein B. How sex and age affect immune responses, susceptibility to infections, and response to vaccination. Aging Cell 2015; 14(3):309-21.
26. Klein SL, Jedlicka A, Pekosz A. The Xs and Y of immune responses to viral vaccines. Lancet Infect Dis 2010; 10(5): 338-49.
27. Klein SL, Poland GA. Personalized vaccinology: one size and dose might not fit both sexes. Vaccine 2013; 31(23): 2599-600.
28. Klein SL. Sex influences immune response to viruses, and efficacy of prophylaxis and therapeutic treatments for viral diseases. Bioessays 2012; 34(12): 1050-9.
29. Engler RJ, Nelson MR, Klote MM, et al.; Walter Reed Health Care System Influenza Vaccine Consortium. Half vs full dose trivalent inactivated influenza vaccine (2004-2005). Arch Intern Med 2008; 168(22): 2405-14.
30. Markle JG, Fish EN. SeXX matters in immunity. Trends Immunol 2014; 35(3): 97-104.
31. Furman D, Hejblum BP, Simon N, et al. System analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. Proc Natl Acad Sci U S A 2014;111(2): 869-74.
32. Kennedy RB, Ovsyannikova IG, Pankratz VS, et al. Gender effects on humoral immune responses to smallpox vaccine. Vaccine 2009; 27(25-26): 3319-23.
33. Troy JD, Hill HR, Ewell MG, Frey SE. Sex difference in immune response to vaccination: A participant-level meta-analysis of randomized trials of IMVAMUNE smallpox vaccine. Vaccine 2015; 33(41): 5425-31.
34. Marvell DM, Parish HJ. Tetanus prophylaxis and circulating antitoxin in men and women. Br Med J 1940; 2(4173): 891-5.
35. Brandão Pires A, de Oliveira TC, de Cunto Brandileone MC, Gonçalves JE, Ikuko Yara T, Simonsen V. Persistence of antibody response to pneumococcal capsula polysaccharides in vaccinated long term-care residents in Brazil. Vaccine 2004; 23 (6): 762-8.
36. Goldblatt D, Southern J, Andrews N, et al. The Immunogenicity of 7-Valent Pneumococcal conjugate vaccine versus 23-Valent Polysaccharide Vaccine in adults aged 50-80 years. Clin Infect Dis 2009; 49(9): 1318-25.
37. Klein SL, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. Trans R Soc Trop Med Hyg 2015; 109(1): 9-15.
38. Voysey M, Barker CI, Snape MD, Kelly DF, Trück J, Pollard AJ. Sex dependent immune responses to infant vaccination: an individual participant data meta-analysis of antibody and memory B cells. Vaccine 2016; 34(14): 1657-64.
39. Martins C, Garly ML, Bale C, et al. Measles antibody levels after vaccination with edmonston-Zagreb and Schwarz measles vaccine at 9 months or 9 and 18 months of age: a serological study within a randomized trial of different measles vaccine. Vaccine 2013; 31(48): 5766-71.
40. Ovsyannikova IG, Jacobson RM, Vierkant RA, Jacobsen SJ, Pankratz S, Poland GA. Human leukocyte antigen class II alleles and rubella- specific humoral and cell- mediated immunity following measles-mumps-rubella-II vaccination. J Infect Dis 2005; 191(4): 515-9.
41. Hayter SM, Cook MC. Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. Autoimmun Rev 2012; 10: 754-65.
42. Cober C, Loisel DA, Gilad Y. Sex-specific genetic architecture of human disease. Nat Rev Genet 2008; 9(12): 911-22.
43. Lamason R, Zhao P, Rawat R, et al. Sexual dimorphism in immune response genes as a function of puberty. BMC Immunol 2006; 7:2.
44. Smith-Bouvier DL, Divekar AA, Sasidhar M, et al. A role for sex chromosome complement in the female bias in autoimmune disease. J Exp Med 2008; 205(5): 1099-108.
45. Seminog OO, Seminog AB, Yeates D, Goldacre MJ. Associations between Klinefelter's syndrome and autoimmune diseases: English national record linkage studies. Autoimmunity 2015; 48(2): 125-8.
46. Jørgensen KT, Rostgaard K, Bache I, et al. Autoimmune diseases in women with Turner's syndrome. Arthritis Rheum 2010; 62(3): 658-66.
47. Tarr T, Dérfalvi B, Győri N, et al. Similarities and differences between pediatric and adult patients with systemic lupus erythematosus. Lupus 2015; 24(8): 796-803.
48. Mina R, Brunner HI. Update on differences between childhood onset and adult onset systemic lupus erythematosus. Arthritis Res Ther 2013; 15(4): 218.
49. Webb R, Kelly JA, Somers EC, et al. Early disease onset is predicted by a higher genetic risk for lupus and is associated with a more severe phenotype in lupus patients. Ann Rheum Dis 2011; 70(1): 151-6.
50. Lashine YA, Seoudi AM, Salah S, Abdelaziz AI. Expression signature of microRNA-181-a reveals its crucial role in the pathogenesis of paediatric systemic lupus erythematosus. Clin Exp Rheumatol 2011; 29(2): 351-7.
51. Tang Y, Luo X, Cui H, et al. MicroRNA-146A contributes to abnormal activation of the type I interferon pathway in human lupus by targeting the key signaling proteins. Arthritis Rheum 2009; 60(4): 1065-75.
52. Ahmed S, Ali SR, Ishaque S, Sami N. Clinical and biochemical characteristics of children with juvenile idiopathic arthritis. J Coll Physicians Surg Pak 2014; 24(7): 498-502.
53. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet 2014; 383(9911): 69-82.
54. Chiaroni-Clarke RC, Munro JE, Ellis JA. Sex bias in paediatric autoimmune disease - Not just about sex hormones? J Autoimmun 2016; 69: 12-23.
55. Ostman J, Lönnberg G, Arnqvist HJ, et al. Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983-2002. J Intern Med 2008; 263(4): 386-94.

56. Bottini N, Musumeci L, Alonso A, et al. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. Nat Genet 2004; 36(4): 337-8.
57. Nielsen C, Hansen D, Husby S, Lillevang ST. Sex-specific association of the human PTPN22 1858T-allele with type 1 diabetes. Int J Immunogenet 2007; 34(6): 469-73.
58. Kahles H, Ramos-Lopez E, Lange B, Zwermann O, Reincke M, Badenhoop K. Sex-specific association of PTPN22 1858T with type 1 diabetes but not with Hashimoto's thyroiditis or Addison's disease in the German population. Eur J Endocrinol 2005; 153(6): 895-9.
59. Bardella MT, Fredella C, Saladino V, et al. Gluten Intolerance: gender and age related differences in symptoms. Scand J Gastroenterol 2005; 40(1): 15-9.
60. Bai D, Brar P, Holleran S, Ramakrishnan R, Green PH. Effect of gender om the manifestation of celiac disease: evidence for greater malabsorption in men. Scand J Gastroenterol 2005; 40(2): 183-7.
61. Volta U, Bellentani S, Bianchi FB. High Prevalence of celiac disease in Italian general population. Dig Dis Sci 2001; 46(7): 1500-5.
62. Wingren CJ, Agardh D, Merlo J. Sex differences in coeliac disease risk: a Swedish sibling design study. Dig Liver Dis 2012; 44(11): 909-13.
63. Ivarsson A, Persson LA, Nyström L, Hernell O. The Swedish coeliac disease epidemic with a prevailing twofold higher risk in girls compared to boys may reflect gender specific risk factors. Eur J Epidemiol 2003; 18(7): 677-84.
64. Wingren CJ, Björck S, Lynch KF, Ohlsson H, Agardh D, Merlo J. Coeliac disease in children: a social epidemiological study in Sweden. Acta Paediatr 2012; 101(2):185-91.
65. Lurz E, Scheidegger U, Spalinger J, Schöni M, Schibli S. Clinical presentation of celiac disease and the diagnostic accuracy of serologic markers in children. Eur J Pediatr 2009; 168(7):839-45.
66. Megiorni F, Mora B, Bonamico M, et al. HLA-DQ and susceptibility to celiac disease: evidence for gender differences and parent of origin effects. Am J Gastroenterol 2008; 103(4): 997-1003.
67. O'Farrelly C, Feighery C, O'Briain DS, et al. Humoral response to wheat protein in patients with coeliac disease and enteropathy associated T cell lymphoma. Br Med J (Clin Res Ed) 1986; 293(6552): 908-10.
68. Herzog D, Buehr P, Koller R, et al.; and The Swiss IBD Cohort Study Group. Gender differences in paediatric patients of Swiss inflammatory bowel disease cohort study. Pediatr Gastroenterol Hepatol Nutr 2014; 17(3): 147-54.
69. Gupta N, Bostrom AG, Kirschner BS, et al. Gender differences in presentation and course of disease in pediatric patients with Crohn disease. Pediatrics 2007; 120(6): e1418-25.
70. Thayu M, Shults J, Burnham JM, Zemel BS, Baldassano RN, Leonard MMB. Gender differences in body composition deficits at diagnosis in children and adolescents with Crohn's disease. Inflamm Bowel Dis 2007; 13(9): 1121-8.
71. Sagiv-Friedgut K, Karban A, Weiss B, et al. Early-Onset Crohn disease is associated with male sex and a Polymorphism in the IL-6 Promoter. J Pediatr Gastroenterol Nutr 2010; 50(1):22-6.
72. Biank V, Friedrichs F, Babusukumar U, et al. DLG5 R30Q variant is a female- specific Protective Factor in Pediatric Onset Crohn's Disease. Am J Gastroenterol 2007; 102(2): 391-8.
73. Browning BL, Annese V, Barclay ML, et al. Gender- stratified analysis of DLG5 R30Q in 4707 patients with Crohn disease and 4973 controls from 12 Caucasian cohorts. J Med Genet. 2008; 45(1):36-42.
74. Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res 2009; 65(6): 591-8.
75. Goldman S. Opinion: sex, gender and the diagnosis of autism – a biosocial view of the male preponderance. Res Autism Spectr Disord 2013; 7(6): 675-9.
76. Jacquemont S, Coe BP, Hersch M, et al. A higher mutational burden in female supports a "female protective model" in neurodevelopmental disorders. Am J Hum Genet 2014; 6; 94(3): 415-25.
77. Robinson EB, Lichtenstein P, Anckarsäter H, Happé F, Ronald A. Examining and interpreting the female protective effect against autistic behavior. Pnas 2013; 110(13): 5258-62.
78. Supekar K, Iyer T, Menon V. The influence of sex and age on prevalence rates of comorbid conditions in autism. Autism Res 2017; 10(5): 778-89.
79. Krull KR. Attention deficit hyperactivity disorder in children and adolescents: Epidemiology and pathogenesis. UptoDate, 2017.
80. Williamson D, Johnston C. Gender differences in adults with attention-deficit/hyperactivity disorder: A narrative review. Clin Psychol Rev 2015; 40: 15-27.
81. Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2007; 61(3): 348-58.
82. Mond J, Hall A, Bentley C, Harrison C, Gratwick-Sarll K, Lewis V. Eating-disordered behavior in adolescent boys: eating disorder examination questionnaire norms. Int J Eat Disord 2014; 47(4): 335-41.
83. Raevuori A, Keski-Rahkonen A, Hoek HW. A review of eating disorders in males. Curr Opin Psychiatry 2014; 27(6): 426-30.
84. Weltzin T, Bean P, Klosterman E, Lee HJ, Welk-Richards R. Sex differences in the effects of residential treatment on the quality of life of eating disorder patients. Eat Weight Disord 2015; 20(3): 301-10.
85. Ahn UM, Ahn NU, Nallamshetty L, et al. The etiology of adolescent idiopathic scoliosis. Am J Orthop (Belle Mead NJ) 2002; 31(7): 387-95.
86. Chan V, Fong GCY, Luk KDK, et al. A Genetic Locus for Adolescent Idiopathic Scoliosis Linked to Chromosome 19p13.3. Am J Hum Genet 2002; 71(2): 401-6.
87. Justice CM, Miller NH, Marosy B, Zhang J, Wilson AF. Familial idiopathic scoliosis: evidence of an X-linked susceptibility locus. Spine (Phila Pa 1976) 2003; 28(6): 589-94.
88. Kulis A, Gozdzialska A, Drag J, et al. Participation of sex hormones in multifactorial pathogenesis of adolescent idiopathic scoliosis. Int Orthop 2015; 39(6):1227-36.

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Correspondence to:
Isabella Tarissi De Jacobis
Dipartimento Pediatrico Universitario-Ospedaliero (DPUO),
UOC Pediatria Generale e Malattie Infettive,
Ospedale Pediatrico Bambino Gesù, Roma, Italia.
isabella.tarissi@opbg.net