Autism Spectrum Disorder according to an integrated multidisciplinary framework

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In recent decades the Western world has been the scene of a profound epidemiological transformation, characterized on the one hand by an evident decline in the incidence of acute diseases caused by exogenous causes (infectious and parasitic diseases), on the other by an equally rapid increase in chronic conditions, degenerative, inflammatory and neoplastic diseases, with a worrying anticipation of the age of onset (Landrigan et al 2005, Burgio 2011). The phenomenon concerns, in particular, endocrine-metabolic diseases (obesity "pandemic", Burgio et al. 2015a); neurodevelopmental disorders (Fombonne 2009) and neurodegenerative diseases (Brookmeyer et al 2007); immunomediated diseases (allergies, autoimmune diseases, celiac disease, Bach 2002); diseaes of the genital and reproductive sphere (Virtanen et al 2005); cancer - in particular children (Burgio 2013a). All these conditions show a parallel growth trend, a real "epidemiological transition", a transformation that is difficult to explain on the basis of traditional epidemiological and etiopathogenetic models. The epigenetic mechanisms provide a more plausible explanation of the phenomenon, compared to genetic models in the strict sense (Gluckman and Hanson 2004). These mechanisms are important topics addressed within pediatric scientific societies in recent years, (*First Thousand Days of Life*)

Among the neurodevelopment disorders, autism spectrum disorders (ASD) are currently a very relevant condition in the developmental age, considering high prevalence, wide variability of clinical presentation, efficacy of therapeutic interventions (if appropriate and well-timed) and the consequent possibility to change significantly the future disability, with positive effects on both the quality of life of the individual and the costs to the community. The increase in prevalence - only partly explained by the increased diagnostic sensitivity - in the USA showed an increase from 1: 1200-1500 to a 1: 150 in thirty years (Centers for Disease Control and Prevention 2007) and from 1: 150 to 1:68 over the past five years (Centers for Disease Control and Prevention 2012), with a much higher prevalence in males (1:54) than females (1: 252). Recent estimates proposed by the Istituto Superiore di Sanità confirm also in Italy a prevalence of 1 in 100 cases.

People with ASD have difficulties in social interaction and communication, stereotypical behaviors and restricted interests. Clinical manifestations are very heterogeneous, especially related to the wide variability of cognitive functioning: from severe intellectual disability to a normal - or much higher than normal - intelligence. The wide range of phenotypic variability and symptomatic overlapping with other neuro-developmental disorders (ADHD, obsessive-compulsive disorders, learning disorders) (Anholt et al., 2010) suggest that these conditions should be considered synaptogenesis disorders and abnormal construction of neuronal networks: so we'd better talk about *software* (connectoma), rather than brain *hardware* (Levy et al., 2009).

A pathogenetic model based on epigenetic rather than genetic in the strict sense, changes the perspective and the framework for research and clinical assistance for autism spectrum disorders. According to this perspective, main topics are considered on the one hand the identification of main environmental disturbing factors for neurodevelopment in fetal and child age, on the other the knowledge about possible pathogenetic mechanisms that can influence the neural network development. Among these mechanisms, inflammation (primary or reactive, endogenous or maternal-fetal) (Estes ML et al., 2016); changes and effects of the maternal-fetal and child microbiota / microbiome (De Theije CG et al 2011); effects of protracted stress (both maternal-fetal and infantile) are the most interesting. Main attention is currently given to the study of the placenta, a sort of "black box of pregnancy", for its central role in fetal epigenetic programming and fetal development. In fact placenta is the setting in which fetus, uterine microenvironment and external environment meet and match each other. The placenta is an important control room of epigenetic molecular

adaptations, in particular as regards the methylation of imprinted genes that play a crucial role in the control of fetal development (Kundakovic et al., 2015).
According to this pathogenetic model, there are important implications for research and assistance.

1. Agreement about the importance of the perturbation of embryo-fetal programming means that this is the fundamental period to determine fragility and disease in the future. If so, effective strategies of primary prevention represent the most important tools to counter the progressive increase of ASD. The identification of the main environmental factors and the pathogenetic mechanisms responsible for the disruption of neurodevelopment should be tha main topic of intervention, in order to change the temporal window of maximum vulnerability (embryo-fetal epoch) into the most important opportunity for health in the future.
A further implication of the epigenetic pathogenetic model is represented by the different ways with which the deviation of the neurodevelopment trajectory occurs and present itself . In fact, ASD can present itself as a lack of acquisition of skills during development (Early Onset), or can manifest itself as a loss of previously acquired skills (Regressive Autism). In the latter case, multiple possible triggers can act and make evident a pre-existing vulnerability. Towards the prevention of such vulnerability - and not so much on the countless possible trigger factors - the maximum commitment of the scientific community should be addressed to counter the progressive increase of ASD and other neurodevelopmental disorders.

2. In people with ASD, interference with epigenetic planning in embryofoetal period often affects not only the central nervous system, but also other organs and systems. The expected consequences of this wider interference is a multisystemic involvement, with a very variable and complex phenotype, in which the behavioral disorder can be influenced by multiple factors that need to be known and considered before planning the psychoeducational and psychopharmacological intervention. Gastrointestinal disorders are more frequent and severe in people with autism than in general population (McElhanon BO et al., 2014) as are frequently reported psycho-neuro-immune-endocrine abnormalities (allergic diseases, above all), sleep disorders, epilepsy (Aldinger et al. 2015). Regarding gastrointestinal disorders, correlation between the severity of these symptoms with the severity of intellectual disability and dysfunctional behaviors raises gastroenterological and allergological competence as a question to be dealt with with the highest priority in people with ASD, as a prerequisite to alleviate painful symptoms often undiagnosed as possible cause dysfunctional behaviors (Heifert 2016 et al). Therefore, the psychoeducative and psychopharmacological intervention in ASD may be set after the identification and treatment of medical comorbidities.

3. Abnormal development of the neuronal network in individual ontogenesis can have consequences on the cognitive, emotional, perceptual, relational and motor levels. Therefore, it is not surprising the overlapping of the different neurodevelopmental disorders (autism, learning disabilities, ADHD, intellectual disability, eating disorders, behavioral disorders). For this reason, in-depth and comprehensive neuropsychiatric evaluations are the prerequisites for the start of effective psychoeducational interventions, in order to plan the multi-dimensional functional individual profile. This is extremely important, for example, in the definition of school didactic programs, in order to suggest teaching proposals consistent with the individual educational needs for each student with ASD.

4. The pathogenetic model based on fluid genomic network with continuous dialogue with the environment, can explain best outcome when early and well-timed psychoeducational intervention is planned and implemented. In fact, in the first two years of life there is maximum neuroplasticity - and therefore, maximum reversibility of the effects of perturbation in intrauterine growth. This is confirmed by the effectiveness of early interventions involving family members and childhood communities

Project

Introduction

The health needs of people with ASD require an adaptation of the care model according to a systemic perspective, through an integrated multidisciplinary approach. This is consistent with scientific evidence and with law requirements (Law No. 134/2015 "Provisions on the diagnosis, treatment and qualification of people with autism spectrum disorders and assistance to families "). Families of people with ASD report lack of competence of health professionals regarding the medical comorbidities, even if these conditions often have a great impact on dysfunctional behaviors. Furthermore, the discontinuity of care in the transition phase from adolecence to adulthood is highlighted as a relevant lack in assistance to people with ASD.

An effective multidisciplinary assistance model is hard to be implemented without a shared cultural background between all the professionals involved in care of people with ASD. For this reason, supporting professional collaboration and synergies between pediatric care centers, family pediatricians network and child neuropsychiatry units - towards psychiatry in adulthood - is the necessary condition and the starting point for the concrete realization of an integrated model of assistance.

The proposal also includes the enhancement of experiences gained by family associations.

Aims

The project aims to promote synergies between available resources, in order to satisfy health needs of people with ASD.

A data collection system will be set up for research purposes.

Furthermore, monitoring the effectiveness of the project is planned.

Methods

A multidisciplinary team will be set up in a pediatric hospital center, including gynecologist, neonatologist, pediatrician, neuropsychiatrist, psychiatrist, gastroenterologist, immuno-allergist, neurologist, clinical geneticist, otorhinolaryngologist. Sharing of the same cultural background will be the first step of the project. Therefore, strategies for diagnostic assessment and intervention for people with ASD will be suggested.

Similar training will be addressed to family pediatricians and neuropsychiatrists of the territorial network..

Training will be divided in two phases:

a) In the first two days a common cultural perspective will be presented to all professionals in the project.

Main topics of training are:

- Neurodevelopmental disorders: fluid network between genome and environment, risk factors and background for the systemic perspective
- Autism spectrum disorders: definition, diagnosis and intervention according to the Guidelines
- Biomarkers in autism: from research to the clinic
- Immune abnormalities in autism, gut-brain axis and neuroinflammation
- Gastroenteric manifestations: diagnosis and therapy
- Pain in people with autism: when to suspect and how to evaluate it

b) Subsequently, different training modules will be implemented according to the specific disciplines involved in comorbidities (in particular, pediatrics, immunoallergology, gastroenterology), by professionals with clinical experience with people with autism

Expected results

The set up of an integrated multidisciplinary network will fulfill the complex health needs of people with ASD, with positive outcomes on the quality of life of patients and their families.

Knowledge about primary prevention, diagnosis and treatment of medical comorbidities and transition towards adulthood will be the main innovative aspects. Consequences on the medium and long term are also expected from synergic collaboration between all the professionals involved in the care, influencing the outcome of future disability and the social costs associated with it.

The proposal provides for the involvement of young doctors in training. In fact, the systemic perspective for ASD, from the pathogenetic model to the wide phenotypic variability, may be an important opportunity for professional growth, for open and ethic minds.

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Fig 1 Modello dell'origine embio-fetale delle malattie *(DOHaD-Developmental Origins of Health and Diseases),* secondo la quale il rapido incremento della maggior parte delle malattie cronico-degenerative e infiammatorie degli ultimi decenni sarebbe il risultato di un mismatch della programmazione epigenetica nelle prime fasi della vita embrio-fetale. (Burgio E, 2016)

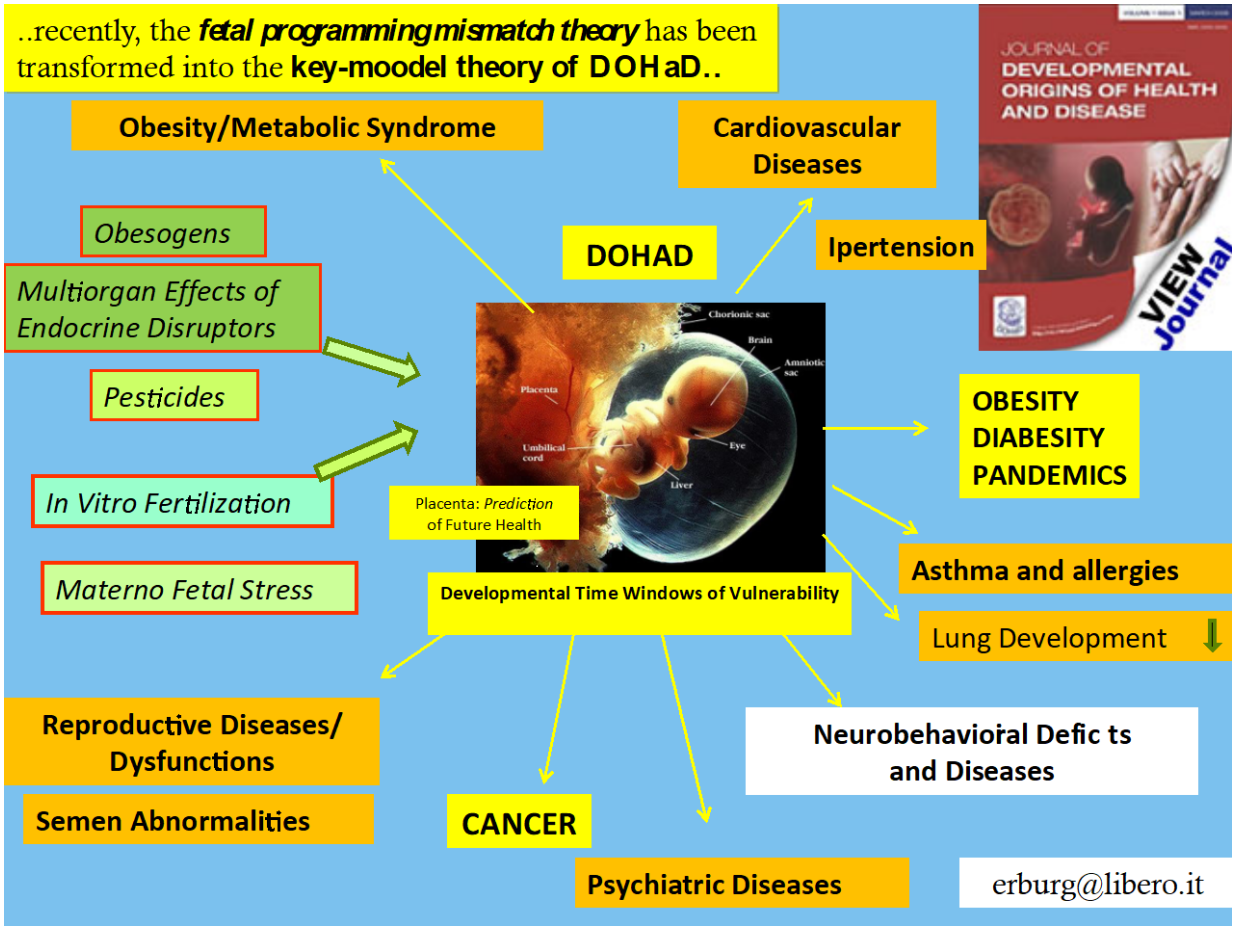

Fig 2 MIA (Maternal Immune Activation) come fattore predisponente fondamentale per i disturbi neuropsichiatrici (Estes ML, 2016)