Critical review

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Effective Clinical Care

Autism Spectrum Disorders through the lens of complex-dynamic systems theory.

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Abstract

Introduction

Autism spectrum disorders are significantly increased in recent decades. Also, it is about a disorder whose aetiology and pathogenesis are largely unknown or unidentifiable. Principles from complex-dynamic systems theory and systems biology could contribute to understand such a complex and multidimensional disease. Aspects about autism, which are emerged from the complex-dynamic systems theory, are discussed and possible hypotheses are formulated.

Conclusion

Autism consideration via complex-dynamic systems approach unfolds the complexity and multidimensionality of the disorder. This approach may help in pathogenesis understanding and the nature course of the disease. Possible predictive factors, also, it is possible to be recognized. New perspectives about disease origin may emerge and personalized therapeutic strategies for each patient may develop. On the other hand, preventive programs may take place. Finally, the aim of autism spectrum disorders therapy must be the maintenance and the increase, if it is possible, of organism complexity and variety, through personalized practices.

Introduction

Autism spectrum disorders (ASDs) have significantly increased in recent decades. A variety of genetic, epigenetic and environmental factors have been implicated, but no one can claim the exclusive and dominant role in the cause of the disorder. Its phenotype is highly heterogeneous and includes disorders of higher cortical functions in humans, affecting communication and sociality, but with varying graduation in each individual and coexistence with other neural (e.g., stereotypy, convulsions, hyperactivity, attention disorders, sleep problems etc) and extra-neural events (e.g., gastrointestinal problems)[1,2]. Finally, the natural process of the disorder itself is heterogeneous, with undetermined prognosis and treatment.

Principles from complex-dynamic systems theory and systems biology could contribute to understand such a complex and multidimensional disease. Nowadays, disease is viewed as a consequence of disease-perturbed networks[3]. The nature of biology is that of a holistic system. This approach mostly applied in "brain diseases" (included autism),[4] in which interactivity and enormous complexity are major features. Basic principles of complex-dynamic systems theory and clinical characteristics of autism spectrum disorders are reviewed in order to push forward novel correlations to understanding the nature of autistic disorder.

Discussion

The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Autism: From reduced connectivity to reduced communication

Reduced connectivity in ASDs

Recent studies have investigated functional and structural abnormalities in brain connectivity. It has been proposed that the deficits in autism are a result of a reduced integration of information due to this underconnectivity and impaired communication between different brain regions. Consequently, a current model proposes ASDs as a developmental disconnection syndrome[5].

Altered neurotransmitters in ASDs

One of the most consistent abnormalities in autism is the altered levels of monoamines (serotonin, dopamine, epinephrine, nor-epinephrine) and other neurotransmitters, such as acetylcholine and glutamate[6]. The alteration in neurotransmitters levels reflects the disconnection that governs the autistic disorder in general.

Impaired systems connectivity in ASDs

Autism is a polygenetic developmental neurobiologic disorder with multiorgan system involvement, though it predominately involves central nervous system dysfunction[7]. Gastrointestinal problems have been implicated in many people with ASDs and there is a possible link between the gut and autism pathogenesis. Disruption of tight junctions leads to intestinal hyperpermeability (the so-called "leak gut") which is implicated in the pathogenesis of diseases such as autism[8]. Particularly, seems to be a link between gastrointestinal symptom severity and autism severity, which gives more evidence for the gut-to-brain connection8. So, it is proposed impaired systems connectivity (brain-gut) in ASDs[9].

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Reduced communication/socialization in ASDs

At clinical level, ASDs are neurodevelopmental disorders that have implications in cognitive impairments, sociability impairments (especially reciprocal social interaction), impairments in communication (verbal and non-verbal), restricted interests and stereotyped behaviours. Autistics do not interact with others, so it is noticed an interruption in circular causality and feedback between the organism and its environment. The concept of circular causality is one of the most important features of balance in biological relativity[10]. Autistics are no more open systems as they don't exchange energy and information across their boundaries with the environment.

Consequently, the reduced/impaired connectivity at lower-scale in ASDs refers to reduced communication/socialization as an emergent property at the higher-macroscopic scale in ASDs. When cells-molecules-networks-systems in the brain or elsewhere cease to connect, individuals cease to communicate.

Autism as complex-dynamical disease

Heterogeneity is major feature of autistic disorder. This means that non-linear, complex, dynamic relationships govern the disorder, since plenty of factors have been no collectively, unpredictably implicated in its aetiology, pathogenesis, phenotypic expression and prognosis. Subsequently, principles from complex-dynamic systems theory could contribute to understand such a multidimentional disease.

Heterogeneity in autism aetiology

Autism aetiology and pathogenesis are largely unknown or unspecified. A variety of genetic (it is thought more than one gene and specific epitopes with varied expressivity), epigenetic and environmental factors have been implicated, but no one can claim the exclusive aetiopathogenetic dominant role in the disorder[1,11]. Moreover, the involvement each of the three abovementioned categories factors in each ASD case is dynamic over time or in other words, each ASD case is personalized in its aetiopathogenesis. Different ASD people can exhibit the same phenotype but arrive at the same "destination" via multiple different, multifactorial pathways. Also, a genetic overlap between ASD, epilepsy and intellectual disability is apparent in many cases[11]. This means that alterations in the same pathway may be involved in different disease phenotypes in order to brain restore homeostasis. So, a systems-level approach of disease evolution is required to incorporate all the myriad factors than can influence such outcomes as autism or other mental diseases and has the potential to accelerate the development of ASD diagnostics and therapeutics[12].

Heterogeneity in autism phenotypic expression

Autism phenotypic expression is highly heterogeneous and includes disorders of higher cortical functions in humans affecting communication and sociality and stereotypies, but with varying gradation in each individual and coexistence with other neural (e.g., convulsion, hyperactivity and attention disorders, sensory abnormalities, sleep problems etc) and extra-neural onsets (e.g., gastrointestinal problems). The great heterogeneity in clinical and phenotypic expression of the autism spectrum disorder is essentially a strategy of the human body to maximize its adaptation to the (sometimes hostile) environment aiming to survive and evolve. Different autism sub-phenotypes are not a sum of different symptoms, but a peculiar, dynamic, non-linear pattern of system self-organization, according to the systems theory. Autism sub-phenotypes represent such the unhealthy attractors where organism as a whole system enters to, in order to cope with different insults (from internal and external environment). In autistic disorder, human organism, as a whole system, functions at the edgy of chaos, where the system exhibit marked sensitivity to initial conditions (the "butterfly effect"), so gravitate towards many (no one) attractors (many sub-phenotypes). The plenty of autism sub-phenotypes indicate that the disturbance is diffused into the human organism and the system "jumps" among different attractors in order to maintain its stability.

Heterogeneity in autism prognosis

Heterogeneity penetrates autism in its natural course also. 3-25% of autistic children develop within normal limits while others show varying graduation disadvantage13. Different predictors have been noticed and this is an area of great interest for researchers and of confirmation of complex nature of the disorder.

Is autism an anabolic state where overdevelopment results in exhaustion of feedback loops and subsequently reduced system performance?

Macrocephaly in autism

Researches have demonstrated that children diagnosed with ASD show an abnormal acceleration of head growth during the first year of life[14]. Macrocephaly possibly suggests neurons overdevelopment, impaired of their pruning and abnormal neural connectivity.

Increased neurotrophic factors in ASDs

Increased levels of brain-derived-neurotrophic factor (BDNF) and other neurotrophic-like factors in autism, suggest that enhanced anabolic activity in central nervous system mediates this brain overgrowth effect[15]. It is interesting that neonatal levels of these factors are decreased and possibly are accelerated afterwards (macrocephaly also observed 1or 2 months after birth). This may indicate impairments of neuroplasticity.

Megalosomy and obesity in autism

Children with ASD are also significantly longer and heavier at the first year of life. Accelerated head circumference reflects a generalized process affecting other morphological features, including weight and height[16] and it is assumed

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that autism possibly is due to a dysregulation of growth factors in general[17]. Children with ASD are also at risk for overweight and obesity later in their life, regardless of medications prescribed and have high levels of many growth hormones (IGF-1, IGF-2, IGFBP-3, GHBP)[18].

Increased leptin levels in ASD
Studies demonstrate increased leptin levels in autism, a finding driven by the early onset autism sub-phenotype[19].

Increased testosterone and extreme male brain theory in autism
ASDs affect females less frequently than males and several sex-differential genetic and hormonal factors (especially testosterone, both foetal and later life level) may contribute. Subjects diagnosed with an ASD have a male: female ratio of 4:1 and among subject diagnosed with Asperger syndrome the male: female ratio is as high as 9:1[20].

It is hypothesized that autism represents an accelerating metabolic state of the organism. So, in autism the organism as a whole system, in order to copy with perturbations and maintain its stability, increases feedback control mechanisms. Constant influence or strength of perturbations results in interlocked positive feedback loops, additional resource demands and system overdevelopment and enrichment (macrocephaly - which constitutes increased brain volume - and increased neurotrophic and other growth factors may represent such manifestations). But, "grow now, pay later": finally, exhaustion of system regulatory feedback mechanisms takes place and system performance is reduced (autistic behavioural symptoms emerge).

Enriched environment in autism: Does it not only a consequence but a cause also of the disorder?

Enriched maternal environment
Many studies have been shown that maternal metabolic conditions during pregnancy such as diabetes, hypertension and obesity may be broadly associated with neurodevelopmental problems in children, included ASDs[21]. Maternal diet (especially high fat diet consumption) and metabolic status play a critical role in programming the neural circuitry that regulates behaviour, resulting in long-term consequences for offspring behaviour. It is also has been hypothesized that the significant enhancement of maternal folate status during pregnancy may be implicated in neurodevelopmental disorders, such as autism[22]. A systemic view of the question may indicate that synthetic acid supplementation in pregnancy reflect an enriched environment, which results afterwards in exhaustion and, subsequently, reduced ability of the organism as a whole system to use its resources. At this point the outcome is the emergence of autistic behaviour of the offspring.

Enriched environment in child
Excess multivitamin feeding in early infancy (another aspect of enriched environment) may be a potential risk factor for autism. Autism is often associated with altered levels of monoamines (serotonin and catecholamines). Excess multivitamin feeding in early infancy, which has become very popular over the past few decades, may be a potential risk factor for disturbed monoamine metabolism and contribute to increased autism prevalence nowadays[23].

Modern urban life style, obesity, diabetes, high fat diet consumption[24] and so on may be significant epigenetic contributors to the recent ASD rise and, in this frame, autism may be represent adaptive metabolism increase program and a "thrifty-less", "over-supply" phenotype, originated from enriched early-life metabolic and nutritional environment, either maternal or the childish itself. Also, in other words, some cases of autism may represent another offspring phenotype of mothers exposed to "toxic" western life style, with high fat diet consumption and reduced exercise activity. If it is so, it is of great importance for early-life nutritional preventive programs for pregnant women and children to be carried out, given that windows of plasticity close early during human development.

Stereotypy in autism: from microscopic reduced complexity to macroscopic increased entropy

Restricted & Repetitive Behaviour in autism: Emergent property that reflects reduced complexity of human organism as a whole system
Restricted and repetitive behaviour (RRB) and thought is the third point of the triad of impairment in autism (the other two are communication and socialization impairment) ranging from stereotypic body movements to ritual to restricted interests.

Restrictive repetitive behaviours are categorized into two clusters: repetitive sensory motor behaviour (stereotyped movements, repetitive manipulation of objects, that are characterized by repetition of movement) and resistance to change/insistence on sameness (compulsions, rituals, insistence on sameness and circumscribed interests, that have a distinct cognitive component characterized by an adherence to some rule or mental set, e.g., needing to have things "just so" and reflect rigidity of inflexibility). This means that autistics respond to different environmental stimuli uniformly and rigidly. This debilitating sameness touches on every aspect of his life and includes eating the same food (food selectivity, food-neophobia and reduced food diversity are major characteristics in ASDs)[25] having the same content and order in conversations. As a result, autistic child is growing in a static environment of his own creation.

Those wrapped up in a periodic, monotonous dynamic are in no shape to adapt to, and cope with, their environment[26]. In other words, in autism the organism as a whole system

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has lost its variety. The outcome is that feelings associated with the presentation of a novel circumstance are dealt with, such as anxiety, but adaptation does not occur. Repetitive-restricted behaviour (RRB) constitutes emergent property of the human organism as a whole system, which represents linearity, reduced diversity, high predictability, decomplexification (reduced complexity) and loss of adaptation of human organism.

However, healthy systems are dynamic and adapt. Loss of complexity, or chaos, is characteristic of disease[10,27].

Fever in autism: a possible paradigm of plasticity and variety (diversity) of human organism as a whole system

Fever as defence adaptive mechanism which represents increased variety of human organism as a whole system

Fever is a primitive immunological response that has had a long phylogenetic history. The widespread occurrence of fever, an energetically expensive phenomenon, is further support for the hypothesis that fever is adaptive defence mechanism and beneficial to the infected host at the most cases. In terms of complex-dynamic systems theory, pyrogenic reaction constitutes part of human complexity and diversity, as enables the organism to copy with hostile environment (for example, infectious agent). Also, the administration of antipyretics and the sequential fever's suppression possibly interferes with normal immune development of the brain leading to neurodevelopmental disorders, such as autism, in certain genetically and immunologically predisposed individuals. There are reports about the use antipyretics, even paracetamol, on the incidence of autism[28]. Probably, paracetamol is not responsible for the growth of the disorder as an aetiological factor (reductionism, linear approach), but the suppression of fever mechanism is (systemic, nonlinear approach).

Fever in autistics

Literature data indicate that probably there are differences in susceptibility to various infections between normal and autistic children. In particular, studies have shown that autistic children have statistically significant fewer fevers compared with normal children[29]. In addition, autistic children tend to have more chronic problems (e.g., gastrointestinal symptoms) compared with normal children[8]. This might suggest that many autistic children have total or partial loss of the body's ability to develop first-line mechanisms, such as febrile reaction, and thus easily pass in the second and third level defence mechanism lines, such as the occurrence of chronic symptoms or the occurrence of infections without fever. On the other hand, clinical case reports have suggested that behaviours of some children with autism spectrum disorders may improve with fever and return to their "autistic state" afterwards the febrile incident[30,31]. This phenomenon may represent the organism dynamicity and plasticity of these children. It has been already hypothesized that possibly there are two subgroups of autistic children, one of the autistics with the possibility of developing fever and the other of autistics with the absence of febrile incidents[32]. If it is real and given that fever is an energy-consuming mechanism, those autistic individuals who do not develop febrile incidents are probably trying to save energy in order to adapt and survive in an evolving environment hostile to them and autistic children who develop fever are at a very critical stage in evolutionary terms, where it is very important not to lose the defence mechanism of fever development. Consequently, the possibility of fever development or not, represents the increased or decreased diversity, respectively, of autistic child as a whole system. Autistic individuals that have not the possibility of developing high fever incidents may not be able to recover from the disorder. If it is so, new therapeutic and/or preventive perspectives for autism may be opened.

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I would like, also, to dedicate this paper to the sick child.

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