

Immune Shock - Chronologic Event in Some Brain Pathology

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Abstract

In this work we try to observe some factors involved in autistic brain disorder and the time relationship. Using imaging and histology related with the evaluation of symptomatology we can have hypothesis to verify. The evidence related to the anatomic structure involved and the relational systems response added to the specific time in which the symptoms arise must be taken in great consideration to have more information about this kind of disorder. In this review work we observed some relevant literature involving the immune system in brain development in order to verify relationship in pathogenesis of autism disorder. We think are relevant in this Pervasive developmental disorder: the time of expression, micro-environment, immunologic status and genetic profile. All these factors can give right response to the next research activities.

Keywords: Autism disorder; Embryology; Immunology; Pathology; Toxicology; Cognitive neuroscience

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Introduction

As showed by imaging autism is a developmental disorder brain growth, involved in young age (that affects over 1% of new births in the United States and about 2% of boys). It is universally accepted that brain development continues after birth and since 25-30 years and Autism seems related with a loss in some brain connection with reduced cellularity. In these periods some immunologic products are being deeply investigated as autism agents' inducers but without evidence of relationship. But Immune shock in a specific brain development temporal phases what kind of effect can produce in example in some neuron or other cell progression?

Why this pathology not involve elder people? Inflammation in elderly are related with this kind of pathology? Why this condition involved relational systems in priority way? (Emotional -relational), have we apoptosis in neurons related these systems more than other systems?

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We can think that after certain growth phases the immunologic control have less interference power in this process but in some other phases the effect can be more evident. Some kind of white cell shift from normal growth in many immunologic process and we can think the same related ad an high immunologic shock. (in balances in normal situational (t cell-b cells and related mediators). Why autism disease present incidence in certain kind of patient (young)?

In normal brain development related to environmental signals as learning and normal growth is observed a general reduction in some un-useful contacts. (Strategy to have more strong system vs a less). But every patient has its own genetic Phenotype and related immunity systems. We can see that the uman Embryology is related to time and local micro-ambient and gradient of intercellular mediators.

Material and Methods

In this paper we use a Review methods, observing some relevant literature to produce a research hypothesis. The same we observe some classic model in embryology, pathology, immunology, neurology and imaging related to this spectrum of disease.

From reference: we have find that: According WEI H., *et al.* "the mechanisms responsible of autism pathogenesis are not understood, studies have suggested that localized inflammation of the CNS may contribute to the development of autism. Recent evidence shows that IL-6 has a crucial role in the development and plasticity of CNS.

Autistic brain disorder is the most severe groups of Neuro-developmental disorders, referred to ASDs, with problems in communication, social skills, and repetitive kind of behavior. Susceptibility to autism is clearly attributable to genetic factors [1-4], but the etiology of the disorder is unknown. Recent studies suggest that a combination of environmental risk factors, autoimmune conditions and localized inflammation of the central nervous system may contribute to the pathogenesis of autism.

Interleukin (IL)-6 was originally found to be a major inducer of immune and inflammatory response. Recent studies and points to a crucial role of IL-6 within CNS. In the CNS IL-6 can trigger the cell responses mediating inflammation responses, Neuro-genesis, gliogenesis, and cell growth, cell survival, myelination and demyelination. IL-6 is normally expressed at relatively low levels in the brain. However, in the presence of brain injury or inflammation, IL-6 is elevated in the cerebral spinal fluid and brain homogenates. Chronic over-expression of IL-6 in transgenic mice causes neuroanatomical and neurophysiological alterations associated with neurological disease. IL-6 and leukaemia inhibitory factor were found to promote astrocytic differentiation of neural stem/progenitor cells [18]. Most recently, Oh., *et al.* demonstrated that IL-6 promotes specific neuronal differentiation of neural progenitor cells from the adult hippocampus.

Recent studies have reported an association of cytokines with autism. TNF- α , IFN- γ , IL-1 β and IL-12 were found to be elevated in blood mononuclear cells, serum and plasma from autistic subjects. Employing a cytokine PCR array, Vargas et al demonstrated that IL-6, TNF α , transforming growth factor (TGF)- β 1 and macrophage chemo-attractant protein (MCP)-1 were increased in autistic brains. In addition, MCP-1, IL-8 and other proinflammatory molecules were also found to be significantly elevated in the cerebrospinal fluid of autistic children. Consistent with the these findings, our studies using a multiple bead immunoassay showed that IL-6, TNF α , IL-8, GM-CSF and IFN γ were significantly increased in the fontal cortices of autistic subjects as compared with the age-matched controls [5]. All these findings suggest that the immune system and cytokines may play important roles in the pathogenesis of autism. However, the mechanisms by which immune dysfunction and cytokine alteration contribute to the pathogenesis of autism remain unknown. In this study, we examined IL-6 in the cerebellum of autistic subjects. Our results: that IL-6 was significantly increased in the cerebellum of autistic patients as compared to controls. In addition, we over-expressed IL-6 in cerebral granule utilizing a viral construct expression approach to study the effects of IL-6 on neural cell properties and synapse formation. Was demonstrated that IL-6 over-expression in granule cells caused an impairment in adhesion and migration properties. However IL-6 over-expression stimulated the formation of granule cell excitatory synapses, while having no effect on inhibitory synapses. This results provide evidence for an association of aberrant IL-6

expression with autism disorder. Impaired neural cell adhesion and migration, as well as the excessive formation of excitatory synapses caused by elevated IL-6 expression could be an underlying cellular mechanism partially responsible for the pathogenesis of autism.

This study demonstrates that IL-6 was significantly increased in the cerebellum of autistic patients as compared controls. And IL-6 over-expression in cerebellar granule cells in vitro impaired granule cell adhesion and migration properties. In addition, we found that IL-6 over-expression stimulated the formation of excitatory synapses of granule cells, while having no effect on the inhibitory synapses. These findings suggest that the elevated IL-6 in the autistic brain could cause an imbalance of neuronal circuits through its effects on neural cell adhesion/migration and synapse formation, and contribute to the development of autism." [1]

- Hu s., *et al.* write that "Cytokines induce neuronal injury via the free radical nitric oxide; the precise mechanism is unclear. We investigated the hypothesis that cytokine-mediated neurotoxicity in primary cultures of human fetal neurons occurs via an apoptotic mechanism triggered by NO. Treatment of mixed neuronal/glial cell in vitro cultures with IFN-gamma plus interleukin (IL)-1 beta for 13 days induced a high output of NO accompanied by neuronal cell loss. The NO synthase inhibitor N-monomethyl-L-arginine (NMMA) significantly attenuated cytokine-induced neuronal loss, confirming the involvement of NO. Cytokine-mediated neuronal cell damage- injury caused morphologic changes and a DNA fragmentation pattern: apoptosis. These findings could lead to the development of new therapies for neurodegenerative diseases involving glia, cytokines, and NO". [2]
- Grunnet LG., *et al.* showed, "Proinflammatory cytokines are cytotoxic to beta-cells and have been implicated in the pathogenesis of type 1 diabetes and islet graft failure. The intrinsic properties in mitochondrial apoptotic pathway in cytokine-induced beta-cell death is unclear. Here, cytokine activation of the intrinsic apoptotic pathway and the role of the two proapoptotic Bcl-2 proteins, Bad and Bax, were examined in beta-cells. Human islets and INS-1 cells were exposed to a pro-inflammatory cytokines (interleukin-1beta, IFN-gamma, and/or TNF-alpha). Activation of Bad was determined by Ser136 dephosphorylation, mitochondrial stress by changes in mitochondrial metabolic activity and cytochrome c release, downstream apoptotic signaling by activation of caspase-9 and -3, and DNA fragmentation.

We found that proinflammatory cytokines induced calcineurin-dependent dephosphorylation of Bad Ser136, mitochondrial stress, cytochrome c release, activation of caspase-9 and -3, and DNA fragmentation. Inhibition of Bad Ser136 dephosphorylation or Bax inhibit cytokine-induced intrinsic pro-apoptotic signaling. Our findings demonstrate that the intrinsic mitochondrial apoptotic pathway contributes significantly to cytokine-induced beta-cell death and suggest a functional role of calcineurin-mediated Bad Ser136 dephosphorylation and Bax activity in cytokine-induced apoptosis". [3]

- From website <http://www.autism-society.org/what-is/causes/> "It is accepted that it is caused by abnormalities in brain structure or functionality. Brain scans show differences in the shape and structure of the brain in children with autism compared to in neurotypical children. In many families, there appears to be a pattern of autism or related disabilities, further supporting the theory that the disorder has a genetic basis. While no one gene has been identified as causing agent, researchers are searching for irregular segments of genetic code that children with autism may have inherited. It also appears that some children are born with a susceptibility to autism, but researchers have not yet identified a single "trigger" that causes autism to develop.

Other researchers are investigating the possibility that under certain conditions, a cluster of unstable genes may interfere with brain development, resulting in autism. Still other researchers are investigating problems during pregnancy or delivery as well as environmental factors such as viral infections, metabolic imbalances and exposure to chemicals.

Genetic Vulnerability Some harmful substances ingested during pregnancy also have been associated with an increased risk of autism". [4]

- J. Watts showed that “Autism is well known as a complex developmental brain disorder with a uncertain pathogenesis. The definitive mechanisms that promote autism are poorly understood and mostly unknown, yet available theories do appear to focus on the disruption of normal cerebral development and its subsequent implications on the functional brain unit. The main conclusion is that although there is not a clear pathway of mechanisms directed towards a simple pathogenesis and an established link to autism on the symptomatic level; there are however several important theories (neural connectivity, neural migration, excitatory-inhibitory neural activity, dendritic morphology, neuroimmune; calcium signaling and mirror neurone) which appear to offer an explanation to how autism develops. It seems probable that autism’s neurodevelopmental defect is ‘multi-domain’ in origin (rather than a single anomaly) and is hence distributed across numerous levels of study (genetic, immunopathogenic, etc.). A more definitive understanding of the pathogenesis could facilitate the development of better treatments for this complex psychiatric disorder.

Neuroimaging has been playing a crucial role in studying autism spectrum disorders (ASD). Among them, Functional Magnetic Resonance Imaging (fMRI) is remarkably noted. fMRI has an important role in understanding neurobiologic basis for autism and autism-spectrum disorders. As a normal and autism affected brain do not have significant size differences, functional neuroimaging modalities are greatly aiding to investigate the functional activation to probe the functional dysfunction of an autism affected brain. Besides, fMRI findings are providing ASD patho-physiologic informations and trying to find the etiology of autism to develop rationally derived and targeted treatments [2]. According to Gabriel S. Ditcher though the findings have considerable heterogeneity but the common are [2]:

1. Hypoactivation in nodes of the “social brain” during social processing tasks, including regions within the prefrontal cortex, the posterior superior temporal sulcus, the amygdala, and the fusiform gyrus;
2. Aberrant frontostriatal activation during cognitive control tasks works relevant to restricted and repetitive behaviors and interests, including regions within the dorsal prefrontal cortex and the basal ganglia;
3. Differential lateralization and activation of language processing and production regions during communication tasks;
4. Anomalous mesolimbic responses to social and nonsocial rewards;
5. Task-based long-range functional hypo connectivity and short-range hyper-connectivity; and
6. Decreased anterior-posterior functional connectivity during resting states.

Recent efforts of neuropsychiatric genetics are being exerted to reveal genetic mechanism or biological pathways underlying autism. All developmental trajectories for brain growth are seen in autism, suggesting considerable heterogeneity in the specific underlying genetic mechanisms affected. About 20 mostly rare genes or gene mutations are discovered that are each involved in a molecular aspect of the development of neuronal connections, the fMRI and genetic findings in autism closed a loop that validated a developmental neurobiological based model of autism. fMRI studies are focusing on further articulation of functional connectivity disturbances, the neural bases of deficits and skills, and the disturbances in higher levels of brain organization related to control and regulation of thinking, feeling, and behaving [5]

- According Nancy J. Minshew, *et al.* “Functional magnetic resonance imaging studies have had a profound impact on the delineation of the neurobiologic basis for autism. Discovery in fMRI technology for investigating connectivity, resting state connectivity, and a default mode network have provided further detail about disturbances in brain organization -behavior relationships in autism disorder.

Recent fMRI studies have provided evidence of enhanced activation and connectivity of posterior, or parietal-occipital, networks and enhanced reliance on visuospatial abilities for visual and verbal reasoning in high functioning individuals with autism. Evidence indicates the altered activation in fronto-striatal networks related to cognitive control, involving anterior cingulate cortex, and altered connectivity in the other resting state and the default mode network. The findings suggest that the specialization of many cortical networks of the human brain has failed to develop fully in high functioning individuals with autism.

This work provides a specification about neurobiologic basis for this brain syndrome and for the co-occurrence of the signs and symptoms as a syndrome. With this knowledge has come new neurobiologically based opportunities for intervention". [6]

- Gabriel S. Dichter. Writed: "ASDS: common themes have emerged, including: (i) Hypoactivation in nodes of the "social brain" during social processing tasks, including regions within the prefrontal cortex, the posterior superior temporal sulcus, the amygdala, and the fusiform gyrus; (ii) aberrant front striatal activation IN cognitive control tasks relevant to restricted and repetitive kind behaviors and interests, including regions within the dorsal prefrontal cortex and the basal ganglia; (iii) differential lateralization and activation of language processing and production regions during communication tasks; (iv) anomalous mesolimbic responses to social and nonsocial rewards; (v) task-based long-range functional hypo connectivity and short-range hyper-connectivity; and (vi) decreased anterior-posterior functional connectivity during resting states." [7]
- Dora Polšek, *et al.* "Autism spectrum disorders (ASD) represent complex neurodevelopmental disorders characterized by impairments in reciprocal social interactions, abnormal development and use of language, and monotonously repetitive behaviors. With an estimated heritability of more than 90%, it is the most strongly genetically influenced psychiatric disorder of the young age. In spite of the complexity of this disorder, there has recently been much progress in the research on etiology, early diagnosing, and therapy of autism. This review provides a comprehensive summary of morphological and neurochemical alterations in autism known to date. Finally, we mention the progress in establishing new standardized diagnostic measures and its importance in early recognition and treatment of ASD". [8]
- J. Blatt, *et al.* "Autism is defined neurodevelopmental disorder that affects over 1% of new births in the USA, about 2% of boys. The etiologies are unknown and they are genetically complex. There may be epigenetic effects, environmental influences, and other factors that contribute to the mechanisms and affected neural pathway (s). Involved brain specific areas in the cerebellum, limbic system, and cortex. Part (s) of structures appear to be affected most rather than the entire structure, for example, select nuclei of the amygdala, the fusiform face area, and so forth. Altered cortical organization, frequent and narrower minicolumns and early overgrowth of the frontal portion of the brain, affects connectivity. Abnormalities include cytoarchitectonic laminar differences, excess white matter neurons, decreased numbers of GABAergic cerebellar Purkinje cells, and other events that can be traced developmentally and cause anomalies in circuitry. Problems in neurotransmission are evident according recent receptor/binding site studies especially in the inhibitory GABA system transmission likely contributing to an imbalance of the system of excitatory/inhibitory transmission. As postmortem findings are related to core behavior symptoms, and technology improves, researchers are gaining a much better perspective of contributing factors to the disorder". [9]
- Zoran Brkanac, *et al.* "Autism has the highest estimated heritability (> 90%) among behaviorally defined neuropsychiatric disorders. Rapidly advancing genomic technologies and large international collaborations have increased our understanding of the molecular genetic causes of autism. Pharmacogenomic approaches are currently being applied in two single-gene disorders, fragile X syndrome and Rett syndrome, which capture many aspects of the autistic phenotype. This review describes the current information state of the genetics of autism disorder". [10]
- Mohtashem Samsam, *et al.* "Autism spectrum disorders (ASD) comprise a group of neurodevelopmental abnormalities that begin in early childhood and are characterized by impairment of social communication and behavioral problems including restricted interests and repetitive behaviors. Several genes have been implicated in the pathogenesis of ASD, most of them are involved in neuronal synaptogenesis. A number of environmental factors and associated conditions such as gastrointestinal (GI) abnormalities and immune imbalance have been linked to the pathophysiology of ASD. Although there is a strong genetic base for the disease, several associated factors could have a direct link to the pathogenesis of ASD or act as modifiers of the genes thus aggravating the initial problem. Many children affected with ASD have GI problems. (As abdominal pain, chronic diarrhea, vomiting, constipation, G-esophageal reflux, and intestinal infections. GI tract has a direct connection with the immune system and an imbalanced immune response is usually seen in ASD children. Maternal infection or autoimmune diseases have been suspected. Activation of the

immune system during early development may have deleterious effect on various organs including the nervous system. In this review paper we have revisited briefly the GI and immune system abnormalities and neuropeptide imbalance and their role in the pathophysiology of ASD and discussed some future research directions". [11]

- According Mark N. Ziats., *et al.*: "In the September 2012 issue of *The Cerebellum*, Fatemi., *et al.* presented an analysis of the role of the cerebellum in autism [1]. While this is an important work, which synthesizes the main findings of cerebellar research in autism spectrum disorders (ASD), we believe there is an alternative hypothesis to the role of the cerebellum in autism.

The conclusion that the cerebellum is pathogenic in ASD is predicated on the notion that the cerebellum functions in the cognitive processes disrupted in autism, although such pathways remain undiscovered. While the cerebellar contribution to higher cognition has been debated for decades, a clear mechanistic understanding of how the cerebellum may integrate with processes affected in autism, such as theory of mind, is not well established-as Fatemi., *et al.* noted. Human studies that have consistently implicated the cerebellum in ASD do so mostly on the basis of volumetric imaging studies, or postmortem histologic and molecular changes, including our own work [3]. However, as opposed to the notion that these changes are pathogenic-which would require an as yet undiscovered mechanism for the cerebellum in the higher cognitive functions affected in ASD-we propose instead that the unique anatomy, physiology, and development of the cerebellum may result in an exaggerated manifestation of the brain-wide pathologic changes that underlie autism, without being causal for the clinical phenotype. In this sense, then, the cerebellum in autism may be acting as an "anatomical beacon" of more subtle changes in other brain regions where the functional pathology actually rests.

The unique anatomy, physiology, and development of the cerebellum make it a distinct part of the human brain. The cerebellum has the highest cell density of any brain area, approximately four times that of the neocortex, and cerebellar Purkinje cells have more synapses than any other cell type by orders of magnitude. As building synapses requires the appropriate molecular "toolkit," the cerebellum's molecular complexity of transcripts and proteins rivals that of the cerebral cortex. Underlying the heightened synaptogenesis of the cerebellum is the need for energy to carry out this process, resulting in oxidative metabolic demand that is similar to the cerebral cortex as well. The implications of these well-recognized cerebellar properties to autism are profound. The ASD phenotype is considered to ultimately result from synaptic dysfunction], which derives from underlying genetic changes that manifest in aberrant RNA and protein production. Additionally, autism has a strong and growing association with related problems in oxidative metabolism. Is it possible that cerebellar pathology in ASD is more evident than other brain areas purely because the cerebellum contains more of the components that are disrupted in autism?

If the molecular and cellular processes that are abnormal in ASD are dysfunctional throughout the brain, then these observations suggest that the cerebellum may have properties that result in an exaggerated manifestation of ASD pathology compared to other brain regions. Therefore, we hypothesize that the cerebellum may not be etiologic in the pathogenesis of autism spectrum disorders; rather its unique anatomic and physiologic properties may accentuate the mechanisms that are aberrant throughout the autistic brain. Consequently, investigations into autism pathology may be more readily observed in the cerebellum because the changes are more obvious than the concomitant changes in other brain areas responsible for the clinical phenotype.

This hypothesis does not diminish the potential importance of the cerebellum to autism research. Harnessing this unique property has serious implications in diagnostic testing, for example with neuroimaging. Diagnostic tests may be able to identify biological changes in ASD patients earlier in life, which is known to correlate with improved patient outcomes [16,17], by focusing on the cerebellum. While cerebellar changes may not directly cause the cognitive deficits of ASD, they could serve as an "internal biomarker" for the more subtle alterations that must therefore be ongoing in other brain areas but would require more sensitive techniques to detect.

Until it is understood how the cerebellum functions in the higher cognitive processes that are abnormal in autism, the field must consider the alternative hypothesis that changes found in the cerebellum of autistic patients are not pathogenic, but rather are collateral manifestations of the cellular and molecular deficits that are present throughout the autistic brain. The distinctive nature of the

cerebellum may exaggerate changes that are more subtle in other brain areas, without being causal of the ASD phenotype. However, such an interpretation does not diminish the importance of cerebellar research in autism, as this unique characteristic may make the cerebellum an ideal diagnostic target". [12]

- Schumann CM., *et al.* "The amygdala is one of several brain regions suspected to be pathological in autism. Previously, we found that young children with autism have a larger amygdala than typically developing children. Past qualitative observations of the autistic brain suggest increased cell density in some nuclei of the postmortem autistic amygdala. In this first, quantitative stereological study of the autistic brain, we counted and measured neurons in several amygdala subdivisions of 9 autism male brains and 10 age-matched male control brains. Cases with comorbid seizure disorder were excluded from the study. The amygdaloid complex was outlined on coronal sections then partitioned into five reliably defined subdivisions: (1) lateral nucleus, (2) basal nucleus, (3) accessory basal nucleus, (4) central nucleus, and (5) remaining nuclei. There is no difference in overall volume of the amygdala or in individual subdivisions. There are also no changes in cell size. However, there are significantly fewer neurons in the autistic amygdala overall and in its lateral nucleus. In conjunction with the findings from previous magnetic resonance imaging studies, the autistic amygdala appears to undergo an abnormal pattern of postnatal development that includes early enlargement and ultimately a reduced number of neurons. It will be important to determine in future studies whether neuron loss in the amygdala is a consistent characteristic of autism and whether cell loss occurs in other brain regions as well". [13]

Results

From literature we have find that autism disorder are involved in young patient, that we have abnormalities (Imaging, histology) in some brain areas, and a complex symptomatology. Genetic and environment can produce some unbalances in brain grow and immunitary situation is involved. Apoptotic signal contribute in brain growth and immunologic shock can unbalance the environment producing abnormalities.

Conclusion

In this kind of disorder we have seen imaging and histologic abnormalities related to specific brain areas involved in a characteristic symptomatology, produced often during brain development and not in elder people. Related to some genetic-immunologic status we can think that immunologic shock with immune unbalances can produce an abnormal or altered micro-environment. Apoptosis is involved in brain growth and influenced by immunologic status. Even if this pathology has been deeply studied by many researcher we think are relevant: the time of expression, micro-environment, immunologic status and genetic profile.

Discussion

Starting from the evidence that autisms are not elder typical pathology and observing from toxicology and embryology discipline we know that the time is relevant in order to predict some kind of congenic pathologies. We have seen that in embryology are relevant genetic informations, the time, micro-environment factors and their specific time relationship.

From toxicology science we know that some toxic substances produce specific toxicity related to the contact time in embryonic-fetal life with minor or major physio-anatomic damage. Many factors are involved as cellular mediators and intercellular signals but also environmental factors that can modify heavily the normal neuronal growth and development or connectivity. We have seen from literature a relationship between immunologic status and some brain condition and that in autism we have a reduced neuron-connections and population in some area.

Immunology is involved in apoptosis process and an immunologic shock in some periods of growth can produce brain abnormality in some area (involved in example in relationship behavior or other disabilities etc). We have seen "The role of IL-6 within CNS development, IL-6 can trigger the cell responses mediating inflammation responses, Neuro-genesis, gliogenesis, and cell growth, cell survival, myelination and demyelination". [1] And Vargas., *et al.* demonstrated that IL-6, TNF α , transforming growth factor (TGF)- β 1 and

macrophage chemo-attractant protein (MCP)-1 were increased in autistic brains. IL-6 over-expression in cerebellar granule cells *in vitro* impaired granule cell adhesion and migration properties [1]

We know that this interleukin is involved in acute inflammation and can act as B-cell activator. And as TNF is related to fever phenomena (fever center in brain). So what is the effect of an immunologic shock with B-cell stimulation or other immune acute modifications? Immune imbalances? In neuron apoptosis? Neuroconnectivity? And related to determine phenotype? We have seen that "Autism has the highest estimated heritability (> 90%) among behaviorally defined neuropsychiatric disorders" And that "Several genes have been implicated in the pathogenesis of ASD, most of them are involved in neuronal synaptogenesis".

We think that in this kind of pathology must be taken in great consideration the timing in evolution of the physio-anatomic modify related to the micro-environment modification in a determinate genetic profile.

Clarifications

This work is not for diagnostic or therapy intent but only to produce research hypothesis

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