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Review Article

Autism Spectrum Disorders between Difficulties of Diagnosis and Misunderstandings of People

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Abstract

Recently, in standard family conditions, unsocial humans with repetitive behaviors attracts increasing attention. Autism spectrum disorders (ASD) with all its behavioral disorders with deficit communication leading to lack in social interaction, obviously, induced central nervous system perturbations. Awareness of caregivers remains the most important factor facilitating the early diagnosis of autism in children. The educated level in some studies did not contribute for solving the problem of people-misunderstand completely, because their awareness depends on education field and their personality. We suggest that deletion of coding and non-coding genes transmitted from mother to son, resulted from oxidative stress due high anxiety levels, induced ASD. The neuroprotective effect of SNL in combination with MEM, DNP, CTP and ARP exhibited by the restoration levels of dopamine, acetylcholine, serotonin and glutamate. Modulations in neurotransmitters and pro-inflammatory cytokines succeed in adjusting stereotypes behaviors of VAP rats and mice.

Introduction

Autism spectrum disorder (ASD) predominance in American children during the last twenty years, with large spectrum behaviors varied between children complicated the diagnosis of autism [1]. The age of diagnosis considered were 36 months, language delay, identified since 2006. The cognitive skills were ameliorated since their surveillance as intellectual impairments, and improved intellectual ability [1]. Programs proposed by home-schools and private schools are not accepted by autism and developmental disabilities monitoring (ADDM).

The demographic study of typically developed children compared to autistic ones, reported a high number of males compared to females [1-5]. In some cases when parents have to be the sole caregivers of their ASD children, it delays the diagnosis [6]. Only some countries discerned the diagnosis problems of autistic children as their behaviors and health conditions are more likely tends to abnor-

malities, the proposed schedules aimed to care more with ASD children before anaesthesia and early COVID diagnosis. Only Questionnaire was proposed in hospitals to identify children with autism in order to solving symptoms of mental disorders, as they need a set plan of care before anaesthesia that even complicated by COVID pandemic [7].

Multiple symptoms of ASD as lack attention and cognitive impairments increased awareness of caregivers. The early diagnosis preserve from bad adaptive behavior, repetitive/restrictive behaviors. As low cognitive ASD manifest high difference and attract more attention, generally diagnosed earlier compared to other children. Maternal cultural field/level are the main factors of diagnosis age of ASD, neurological diagnosis could contribute as previous medical experience gave good guidance for first steps of diagnosis.

Glutamate Disorders of ASD

Interference of proportions of enzymes involved in glutamate synthesis and metabolism in hippocampus noticed in ASD. A recent study carried on autistic rats showed the increase of glutamate in synaptic cleft and astrocytic glutamate transporter GLT1 of adult rats [8]. We suggest that the increase of glutamate in astrocytes as potential source to assess brain dysfunction resulted in a decrease of glutamine synthetase.

Serum of adult patients of ASD marked high levels of glutamate, with no change in glutamine and glycine [9], interactions between glutamate and TNF-α considered as inflammatory-inducer, but, the increase of glutamate levels in brain result in dysfunction-induce. Under the increased concentrations of glutamate, functional Magnetic Resonance Imaging (fMRI) showed lack of function between the dorsal anterior cingulate cortex of adult males and temporal fusiform cortex, parietal and limbic system, parahippocampal gyrus and temporal pole [10]. Lower levels of glutamate in some brain regions are ASD behaviors-inducer, decrease of glutamate in anterior cingulate cortex (ACC), and striatum induced repetitive behaviors [11].

Gamma amino-butyric acid GABA disorders

ASD as any brain disease raises questions about the intact volume of brain regions and the typical number of main receptors. 83 regions of the brain had lower levels of the α5 receptor in nucleus accumbens and subcallosal area, with no difference noticed in hippocampus where α5-subunit constitute 25% of GABAA receptors, among the three region studied amygdala and nucleus accumbens bilaterally reduced [12]. Recent study tried enhancing GABA-A receptors in brain with ASD. Highlighting the state of excitation/inhibition process. Glutamatergic neurotransmission did not altered in medial prefrontal cortex (mPFC), with no change of excitatory postsynaptic currents, the input-output (I–O) curve decreased and paired-pulse ratio (PPR) increased, and reduction level of GABA from mPFC to cerebrospinal fluid [13].

Pyramidal (Pyr) neurons are targeted by the interneurons "chandelier cell" that decreased in ASD, their importance being in the number of Pyramidal neurons they innervated, a decrease for more than the moiety in $GABA_AR\alpha 2$ protein of excitatory Pyr in the supra granular layers of Brodmann Areas BA9 and BA47 [14]. Hong (2020) and his team confirmed that the decrease in chandelier neurons weaken Pyr-$GABA_AR\alpha 2$ protein production. Autistic mice exhibited crooked tails, had less number of Purkinje neurons in multiple cerebellar lobules leading to reduction of cerebellar volume. Reduction in Purkinje neurons is owing to lack of both synthetic enzymes and transaminases of GABA and glutamate transporter, in molecular layers [15]. Amelioration of GABA-synthetic enzymes in cerebral cortex did not implicated in lessen ASD symptoms of mice. Behavior alterations measured and detected over time, but still the diagnosis remain ambiguous and doubtless, and mostly mixed with other nervous system disorders. The more studies being meticulous using new techniques, the more diagnosis problem easier settled. Even the high Purkinje cells density, the small size of their soma in cerebellum impedes quantification of the signal, an inhibitor of unfolded protein response (UPR) applied to cerebellar slices blocked the increase of miniature spontaneous excitatory postsynaptic currents (mEPSC) [16].

Vitamins deficiency and ASD

A lack in protein levels of retinoic acid receptor-α RARα and Retinol, with failed of their enrichment was revealed with vitamin A deficiency group compared to vitamin A normal group [17], that reinforced the idea that ASD is vitamin A deficiency-related. High

levels of leukocytes and neutrophils, and slight elevation of the pro-inflammatory marker C-reactive protein CRP assessed with lower amounts of 25-OH-Vitamin D. lack of vitamin D, was negatively correlated with leukocytes, neutrophils and CRP [18]. We suggest that vitamin D has been used in first stages of pro-inflammation in ASD, as it could accompanied with deficiency of some other vitamins fat-soluble, as neurodevelopment is fat dependent.

Symptoms

Even positive self-esteem of autistics; disclosing their identity to people in different manners, they abstain from dealing with health persons [19]. Macrocephaly and motor deficits were reported in autism, with all definitive symptoms at two years old [20], but diagnosis of autism generally delayed until the age of three or four years. Premature children were more sensitive as manifested more global, gross motor, social interaction and language delayed [21].

Diagnosis Difficulties of ASD

Alteration of behavior skill

There was difficulties in male diagnosis as females characterised with more social skills, which attract attention of their caregivers and quicken diagnosis. Females were diagnosed at 3 years old and males at 3.5 years, females were more delicate as marked a higher percentage in motor and developmental delay than males, and 48% of children with different grades of intellectual disability [21]. Higher levels of autism symptoms, appeared at young age with less cognitive ability impose more hours of interventions that could responded only by parents with higher education level offering particular states of living [22], helped in preventing aggravation of the disease, in some cases, it related to consciousness and strictness depending to their personality. Diagnostic Behavioral Assessment for ASD – Revised (DiBAS-R) indicated that only when ASD is accompanied with moderate or severe intellectual disability, symptoms elevated compared to mild intellectual disability, and more than 85% participants with intellectual disability or ASD had hearing impairment [23]. Irregular social interaction, obsessive concerns and noticeable thumping body movements. Measuring child behavior checklist (CBCL) high Repetitive Behavior Scale (RBS) and short sensory profile (SSP) noticed in autistic children with both DSM and distinct anxieties, and communication disorders in social responsiveness scale (SRS) [2]. Analyses of eye movement during‘ interfaces use by autistic participants’ were less intelligent than non-autistic users, as their preference tends to images and icons than texts [24]. Autistic group took long time to focus on the highlighted area of interest, then interested in irrelevant elements and had no precise choice during the four tasks when they asked to choose pathway with least number of inter changes, those results reflects that autistic participants spend more time making tasks for failing at the end of tests.

Healthy children valued showing symptoms of ASD children if their parents had greater broad autism phenotype (BAP). Maternal BAP create a discordance of diagnosis parent-teacher, when mothers with BAP esteemed minor anxiety of their children as severe symptoms of autism [25]. While, healthy children with no stereotyped behaviors of autism will obliged their teacher to social responsiveness scale (SRS)-score due the distressed living states offered by BAP parents. Risk of white students to develop autism is three-fold more than other students, but either the caregivers speak English or other language as Spanish appeared decisive in identifying the disease early. 78% of caregivers speak-English proclaim the first signs of autism in children, while only 14.7% of caregivers speak-Spanish proclaim the first signs of autism, and 82% teachers or only school staff are able to notice first early signs of disability in autistic children [26]. Away from wrong reasons revolving around autism as vaccines, lack of mother care. The birth of ASD-children seek for amplified-attention from caregivers and excuse of the society. less than half of American participants, declared that restrictive diets are not crucial for autistic children care as social awareness are, the advantage of their understanding that autism almost associated, but misconceptions as “autistics are nonverbal persons” remains worrying [27]. The nature of autistics as their “routines preference and respect, weird use of objects and difficulty of oneself express” let them appeared futile and will be neglected [27]. The less awareness of participants and fail of teachers to diagnose their students confirmed that people of all countries should be informed first then we will be rated.

Dispersion of alterations in different brain regions

In autism some cerebral regions are affected in males as females but others are affected differently. Rightward deviations of females are amygdala, putamen, and parahippocampal gyrus, while in males were hippocampus and middle temporal gyrus, but leftward deviations of females are frontal pole, orbit frontal cortex, and postcentral gyrus, while in males were temporal pole, lateral occipital cortex, and thalamus [28]. In other hand, regions showed highest overlap in both females and males were multiple as gray matter asymmetry, left cerebellum and lateral occipital cortex and right angular gyrus, middle and inferior temporal gyrus, and superior parietal lobule [28], in accordance with Laidi team, found no difference of cerebellar abnormalities between sexes. There is no difference between sex concerning cerebellar anatomy abnormalities [3]. There was a positive relation between Crus I, postero-inferior lobe and the anterior lobe of the cerebellum [3], in other hand, no cerebellar lobules or heterogeneity difference related to cerebellum was noticed. Small volume of right amygdala in autistic children had revealed in longitudinal magnetic resonance imaging scans [2]. Autistic children with only distinct anxieties had a delay of longitudinal development of right amygdala. When ASD associated with DSM children had a large right amygdale [2]. There were a decline in spike of action potentials; amplitudes of initial and middle of action potentials, and inevitable time of repolarization phase were decreased in CA1 pyramidal neurons, neurons of CA1 of hippocampus contain only few scattered Golgi-like ones [29]. Liao X2020 [30] see the implication of NF-κB in some widespread neurological disease as ASD will open future works, as it may will be future biomarker in early clinical diagnostic. It incite searchers for performing the correct immunological cell pathway as novel therapeutic strategy.

Genome alterations of ASD children

Even the genetic-similarities of cerebellum, brains react differently. We found some differences between nations, In Rome, increase in the volume of lobule VI, but in Cambridge, increase in the volume of Crus II was observed [3].

Involvement of some mutative genes has been established in inherited risk of autism. Sequencing of whole genomes of autistic families, in order to identify mutations, experimenters integrated copy-number variant (CNV), and whole-exome sequencing (WES). The enrichment of private disruptive and de novo mutations of hypersensitive sites of DNase related with autism disease [31], was a key marker of implications of genomes in autism. The transmission from mother to son, of WNT7A gene with suppression of its promoter and first exon, deletion of noncoding genes DSCAM, TRIO, and affection of neurodevelopmental genes SCN2A, CACNA2D4 and ARID1B [31], were the main deletions of genes resulting in high risk of autism transmission from mother to son. Genes corresponding to proteins classified according to their roles, when it consists chromatin regulation or involved in synapse, absolutely, genes will consider as crucial in some diseases. de novo mutation in families with ASD was studied the copy number variants (CNVs) by Simons Simplex Collection (SSC), in more than 2500 families, gene-deletion of 3q29 and SHANK3, lead to 65 risk genes of ASD [32]. Genotype differences were commonly in cerebellum and hippocampus in Fmr1 and 16p mice but in Shank3 mice differences in cerebellar peduncle, pontine nucleus and habenular commissure [33].

Cortical thickness of ASD is related to gene-expression of the glutamate and GABA pathway, where glutamate genes underlyed autism characteristics, but GABA genes are sensory processing associated [34]. The four altered GABA subunits were GABA-A, GABA-A1, GABA-A2 and GABA-A3, with reduction in receptors and gene expressions of both GABA-A and GABA-B mPFC [13]. Recent study showed mutation of synaptic protein NLGN3 in cerebellum as marker of ASD [16]. Niarchou et al., (2022) negate any relation between clinical study and genomes of insomnia, as people had no relation between genes of insomnia and sleep problems, neither minor allele count, concerning people with or without autism. Autism either associated with insomnia or not, any variation of circadian genes has analysed, as there were any correlation between clinical study of insomnia and polygenic scores of main melatonin genes as Basic Helix-Loop-Helix Family Member E41 (BHLHE41) gene [35].

Recent study analysed gene expression and intestinal microbiome associated with ASD. Weakened density and length villi, of VAP-prenatally exposed mice, and less in gene expression of tight junction proteins, and principal-coordinate analysis (PCoA) revealed the alteration in microbiota composition as deficiency of main anaerobes as *Bifidobacterium* and *Coprococcus* [36].

Maternal stress related to ASD risk

As VAP prenatally exposed rats and mice elicited maternal immune responses. The supposition that pro-inflammation neutrophil extracellular traps (NETs)-induced result in provoking cerebral foetuses diseases, due their permeability through blood-brain barrier [37], could be accepted.

Rats prenatally treated with VPA showed lower interest to novelty, and less nociception sensitivity, that referred to lack of organelles in CA1-neurons of hippocampus. Hippocampus integrity assessed by novel object recognition (NOR) test, the short-term recognition memory, revealed the inability of autistic rats to recognize the novel object [29]. Recently, several studies revealed behavior alterations in animals. The increased latency of hind paw interaction in hot plate test, reflect raising in nociceptive threshold and deficit cognitive [29]. Grooming test and three chambers behavioral test are main tests to figure out repetitive behaviors, and social interaction impairment, as main characteristics of autism. VPA treated mice had any preference for new mouse/empty cage indicating its less social interest/interactions [15]. Mice prenatally exposed to valproic acid (VAP) showed impairment of social approach and no preference in social novelty, no locomotor activity changes in open field test, with slight anxiety in plus maze test but enhanced memory in object recognition test. Repetitive behaviors as burying marbles during marble-burying test and self-grooming time [13, 17].

Distance, speed and stretching in OFT deny any anxiety symptoms. The oxidative stress is raising as its markers malondialdehyde (MDA) and H_2O_2 found with higher levels, and decrease of all of glutathione peroxidase (GSH-Px), catalase (CAT), glutathione (GSH) and total antioxidant capacity (TAOC), which reflects the shortage in antioxidant capacity [36]. IL-1β, NFκB and inducible oxide synthase (iNOS) upregulation indicated the inflammation response. SOD supplementation reversed all beahvior and intestinal oxidative stress [36] that confirmed the direct correlation between cerebral regions alterations and increased oxidative stress.

Aggravation of ASD with other symptoms

Naturally, symptoms of ASD aggravated when co-existed with other psychological disease. In the case of obstructive sleep apnea (OSA) symptoms combined with ASD ones children showed behavior abnormalities as new signs of cognitive dysfunction, immoderate sleepiness during the day, insomnia/restless sleep at night resulted in morning headaches [4]. Severity of autism overlapped earlier when associated with OSA, obstructive apnea-hypopnea index was high in severe OSA/autism range only [4]. While studying different types of insomnia as sleep maintenance, short sleep duration and sleep onset, white participants were more than blacks aged between 6 to 30 years, where sleep maintenance is the most common with 81% followed by sleep onset with 72.6% [5], only 11% complain of any type of insomnia. Patients had sleep problems as daytime sleepiness, seizures, parasomnias and bruxism especially, snoring and restless sleep when different types of insomnia co-existed. Melatonin treatment improved sleep problems [5]. Parents trying to offer bed-comfort to their children with ASD, used high quality of bedcovers, sheets and sleepwear, but more than 78% of them reported problems of sleep in their children, as nightmares, restlessness, and feeling too hot [38]. We suggest that respiratory problems of children are the main cause of sleep problems as woollen blanket considered less convenient for sleep. Children take their mealtime regularly and play more than 2 hours a day, but the use of screen surfaces decreased hours of their sleep [38]. So we can assume that respiratory problems with high delicacy of children with ASD to magnetic field of electronic devices and rays disturbs their circadian cycle. A study confirmed that emotion dysregulation (ED) of ASD children showed as frequent reactivity as crying, difficult to calm themselves, but deny dysphoria symptoms as the refuse of doing some activities and absence of reaction to good things happened [39]. Diagnosis of ASD with epilepsy in three fourth pre-schooled males than females, only 13%ofelectroencephalography (EEG) abnormalities in three focal regions were related to epilepsy and received neuroleptic treatment [40].

Treatment of ASD

Protocols proposed by therapists as duration of session, types of questions, exercises offered to patient seemed more efficient in reducing autistic mannerisms. Therapists grateful to protocol of treatment, exercises followed by the patient, and frequency of sessions patient-therapist. Preferably with duration 54min, and enhancement of cognitive flexibility, communication and autistic mannerisms 'self-reported' decreased significantly in post-assessment [41].

Medications as paracetamol taken by participants with autism, methylphenidate hydrochloride is the dispensed medication at persons with attention deficit hyperactivity disorder (ADHD), and ASD and ADHD group. All participants of ASD, ADHD, ASD and ADHD and control take melatonin have more tendency to odd of polypharmacy, and females from deprived areas have more intellectual disability, and those from town had high tendency to odd of polypharmacy [42].

Treatment by solanesol (SNL), aripiprazole (ARP), memantine (MEM), citalopram (CTP), donepezil (DNP) improved the long-term memory, the walking balance, alleviate the depressive behavior so that was a whole spectum indicating its efficiency in recovering neuro functionality affected by the neurotoxin propionic acid (PPA). After intracerebroventricular administration of PPA-autism induced, injection of SNL, ARP, CTP, MEM, and DNP reversed the decrease of ambulatory movement, increase time spend in target quadrant in Moris water maze, decreased time of immobility in forced swimming test [43], indicating behavioral improvement. And restored the weight of rats, decreased the number of slips in muscles, the homogenate of brain had high levels of serotonin, dopamine, acetylcholine, and low level of glutamate, and attenuated pro-inflammatory cytokines TNF-α and IL-1β, in one hand and unblock the antioxidants GSH and SOD, and attenuated MDA, LDH, AchE, and nitrite [43], indicating the restoration of brain and muscle cells due the reactivation of antioxidant process.

E100 demonstrated antagonist affinity toward histamine H3 receptor (H3R), but affinity at hH1- and H4Rs 10-fold lower, E100 and DNP reduced percentage of shredded nestlets [44]. This result confirmed the reversing effect of repetitive compulsive behaviors VAP-induced. Autistic rats treated with E100 spent more time in centre of open field arena [44], indicating the anxiolytic effect of E100. The E100 or DNP reached to mitigate the increase in proinflammatory cytokines IL-1β, IL-6, TNF-α, and TGF-β [44]. Lysates from hippocampus and cerebellum after exposition to E100 showed a noticeable decrease in the expressions of all of cyclooxygenase-2 (COX-2) , induced nitric oxide synthase (iNOS), and nuclear factor kappa-light-chain-enhancer of the activated 'lymphocytes' B cells p65 subunit (NF-κB p65) and the activated microglia [44], due the chemical modulations, E100 and DNP succeed in reducing repetitive/stereotyped behaviors.

Treatment of mice with clonazepam (CZP) as GABA-A receptor agonist and baclofen as GABA-B receptor agonist, when they introduced via mPFC-cannula implanted were efficient, and reversed all behaviors alterations [13].

Treated mice with oxytocin shaped alterations in cingulate cortex, different regions of cerebellum, and regions sensory/motor behaviors-correlated as cuneate nucleus, superior olivary complex and dorsal teniatecta [33].

Conclusion

ASD degree/severity behaviors and educated level/field of caregivers are decisive for an early diagnosis, to prevent symptoms aggravation. Recent researches carried on genomes confirmed the deletion of mother's genes 'in males' are the main cause induced ASD in children, but we suggest that mutations resulted from oxidative stress. Suggested treatments to regulate neurotransmitters as CTP, DNP and CZP were efficient.

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