PROBABLE ETIOPATHOGENESIS (SAMPRAPTI) OF AUTISM IN FRAME OF AYURVEDA IN RELATION TO INTENSE WORLD THEORY

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Received: 10/05/2013; Revised: 26/05/2013; Accepted: 30/05/2013

ABSTRACT

Autism is one of the pervasive developmental disorders (PDDs). The disease affects the child's interaction skill with the world by involving social responsiveness, communication ability and lack of understanding for the other people showing heterogeneous clinical features of the disease. Hence, to establish the etiopathogenesis (samprapti) of autism will help to interpret its heterogeneity and to frame out its respective management. Hence, an effort has been made to explain the neurobiology of autism on the basis of Ayurvedic fundamentals and ‘intense world theory’ of autism. This knowledge of etiopathogenesis may reveal the specific nature of brain dysfunction in autism and may help to understand the development of symptomatology of the disorder and further its precise nature to respond with various treatment strategies described in Ayurveda.

KEY WORDS: Autism, PDD, etiopathogenesis, intense world theory

Cite this article:
INTRODUCTION

According to DSM-IV, (Diagnostic and Statistical Manual of Mental Disorders, 1994) “Autism is a severe developmental disorder characterized by abnormalities in social functioning, language and communication and unusual interests and behavior”. The key features of autism are –

- Deficient non-verbal behavior such as eye to eye gaze, facial expression, body posture and gestures.
- Failure to develop peer relationship.
- Failure to share enjoyments interests or achievements with other people.
- Impaired development of social language.
- Echolalia/ idiosyncratic language.
- Restricted repetitive and stereotyped patterns of behavior, interests and activities.

Here, the process of the development of symptomatology of autism is tried to explain on the basis of ‘Intense World Theory’ (Markram & Markram, 2010) of autism and fundamental principles of Ayurveda contributing in disease process.

AIMS AND OBJECTIVES

- To validate the contribution of components of Samprapti (etiopathogenesis) (i.e. khavaigunya, tridoshas, trigunas etc.) in pathophysiology of autism.
- To establish the etiopathogenesis of autism in frame of Ayurveda to understand the development of symptomatology so as to avail the multimodal treatment approaches of Ayurveda in management of autism.

REVIEW OF CONCEPT

According to fundamentals of Ayurveda, Samprapti (Etiopathogenesis) of any disease comprises the vitiated dosha-dushya sammurcchhana (union). These vitiated components are manifested in full flown disease, when they merge with already existing ‘khavaigunya’ (Shastri Kaviraj Ambikadutta, 1995) (i.e. structural and functional alteration of body tissues/ system etc.). An etiopathology of autism seems to be evolved with contribution of khavaigunya in greater extent (Flowchart- Step2). Few etiological factors may be consequent as khavaigunya in following way-

i. Genetic Factors: Various research studies establish the direct link between genes and their consequence into autism. Some of them are briefly mentioned here (Flowchart -step1)

- Over expression of NMDA receptor gene, particularly the receptor subunits NR2A and NR2B as well as the CAM Kinase linked second messenger pathway are observed in autistic brains. (Rinaldi et al., 2007).
- Several studies indicate the involvement of glutamatergic systems in autism. Single nucleotide polymorphism (SNPs) in the gene encoding ”glutamate6 receptor” (GLUR6 -Jamain et al., 2002) and “glutamate8 receptor” (GLUR8 - Serojee et al., 2003) were reported in autistic brains. Also, several glutamatergic synapse gene mutations on chromosome 22 were also associated with autism (Jamain et al., 2003).
- Rett’s Syndrome (RTT), a trait of autism, is an X-linked dominant progressive neurodevelopmental disorder which exhibits all the three core characteristics of autism. It is caused by mutations in the gene encoding methyl CPG-binding protein (MeCP2). (Amir et al., 1999)
- Similarly fragile X-syndrome is another X-linked disorder which displays the features similar to autism such as abnormal speech pattern, stereotypic movements and abnormal social behavior, particularly shyness and limited eye contact. It is caused by the mutations in the FMR1 gene that encodes for fragile X-mental retardation protein (FMRP).
Flow chart 1: Probable Etiopathogenesis of Autism
ii. Epigenetic toxic insults: (Flowchart-step2)

- A recent study of autism provides a link between hyper-activation of NMDA receptor and deficiency of hypothalamic inhibitory hormone i.e. digoxin. Lack of digoxin may fail to avoid brain damage due to excitotoxicity (Kurup & Kurup, 2003) and consequent in autism due to toxicity reasoning.

- Imbalance of inhibition-excitation activities of neuronal pathways due to altered levels of serotonergic, GABAergic and NMDA neurotransmitters level may result in epigenetic toxic insults.

iii. Postnatal environmental factors: (Flowchart-step3)

Several perinatal environmental factors may cause autism. These factors include obstetrical complications, prematurity, hypoxic-ischemic encephalitis, jaundice etc. MMR Vaccine and certain drug toxicity are causally linked to the development of Autism.

Thus, above three etiological factors are responsible for the structural and functional alterations in brain (Khavaigunya). This will further activates the molecular imbalance in cellular and circuit level that sensitizes gene expression pathways to respond excessively to environmental stimulation. (Flowchart-step4)

Under normal condition, gene expression pathways would enable for enriched environments to nurture brain development but if these pathways are sensitized then environmental stimulation may cause exaggerated and accelerated development of brain. This will further affect the neuron connectivity in autistic brain. Several MRI studies suggest that in autistic brain long-range connections (essential for complex information processing of higher order functions) between different brain areas are underdeveloped while the short-range connections (essential for primary information processing) are overly developed. (Just et al., 2007; Mottran et al., 2006)

According to Ayurvedic perspective to maintain proper connection between body tissues is a function of pranavayu (i.e. sandhankar karma) (Chaturvedi G. & Shastry K., 1996). Therefore, the hyper-connectivity between short-range synapses and under-connectivity between long-range synapses may be caused by vitiated pranavayu. Similarly to maintain the intactness between these connections or of body tissues is a function of kapha dosha (i.e.sneha, bandha & sthiratva) (Chaturvedi G. & Shastry K., 1996). But the impaired kapha dosha may lack to provide nourishment (Snehana) to brain matter and affects its compactness and stability which ultimately makes brain tissues more vulnerable to endogenous cytotoxicity.

Thus, these alterations in neural connectivity leads to cascade of events which comprises the symptomatology of autism in a following way-

A. Hyper-connectivity to short-range primary sensory pathway

Due to hyper-connectivity between short range neurons, the flow of primary sensory information speedily transfers via synapses causing hyper reactivity across different brain regions (Flowchart-step 4, 5, 6). In Ayurvedic context, this process is carried out by enhanced ‘chalatva guna’ (quality) of vata dosha (Chaturvedi G. & Shastry K., 1996).This hyper-reactivity contributes central role in pathophysiology of autism, which can be interpreted as below–

i. Locus Coeruleus (LC):

Super-charged micro circuits in primary sensory area may produce enhanced sensitivity to sensory stimulation. This may consequently over sensitize to locus coeruleus for upcoming environmental stimulation and may result into enhanced nor epinephrine secretion, which further leads to over excitation of NE pathway (Flowchart-step7).

Over excitatory NE pathway is cause for hyper-perception and hyper-attention. As per a scientific study, higher sustained attention is reported in autism as compare to control group
i.e. autistic people have the ability to maintain attention to repetitive stimuli over prolonged periods of time (Johnson et al., 2007). This may hamper the capacity of selective attention for relevant sensory stimuli and thereby sensory overload. (Flowchart-step8)

- In an Ayurvedic context, vitiated pranavayu and kapha dosha may lead to impairment of function of manas (Chaturvedi G. & Shastry K., 1996) and the function of dhee (Chaturvedi G. & Shastry K., 1996) which result into abnormal orientation and engagement of all relevant and irrelevant environmental stimulation, in turn causes for sensory overload.

ii. Neocortex and Amygdala:

In pathophysiology of autism, neocortex particularly prefrontal and somatosensory cortex and amygdala are involved in great extent. At neocortical region, the hyper-excitatory NE pathway are inhibited by increased GABAergic pathway indicating that inhibition may able to recruit a constant matching level of excitation without developing an imbalance (Rinaldi et al., 2008). This will confront the neocortex for excessive processing of primary sensory information. (Flowchart-step9)

This can be illustrated by an example of sensory perceptions. Primary processing of environmental stimuli of sensory origin (i.e. visual, auditory, touch etc.) may be carried out excessively by somatosensory cortex while cognitive functions related to simple feature are carried out excessively by prefrontal cortex. Similarly, Amygdala may also become overly reactive for processing emotionally relevant information. It is widely established that the amygdala mediates the formation and storage of fear memories (Le Daux, 2003) and enhances memory formation throughout the other brain regions by acting as an emotional amplifier (Cahill & Mc Gaugh, 1996). Hence in autistic people, dysfunction of amygdala may result into exaggerated and more persistent processing and storage of aversive emotional and fear related memories. This is supported by the theory of imbalance of excitation inhibition which would result into increased reactivity, due to loss of inhibition at amygdala (Casonova et al., 2003).

Thus, the hyper reactive neocortex and amygdala may significantly consequences into excessive perception, attention, learning and emotionality (Flowchart-step10). This process of hyper learning is stored in the form of simple features of touch, sound, light, fear, emotions, language etc. (Flowchart-step11).

Hippocampus, Basal ganglia and amygdala are the sites, where memories of these simple features are allocated (Flowchart-step12). Long term potentiation (LTP) is the neuronal mechanism which is widely assumed to underlie memory formation. This LTP mechanism is mediated by glutamatergic neurotransmitters and receptors system particularly NMDA (Nicoll & Malenka, 1999) and alterations in this system may contribute to the above observed hyper-plasticity leading to hyper-memory and hyper-learning. (Flowchart-step13)

With excessive learning and memory processes, sensory regions may consolidate into overspecialized modules and lead to hyper-preference processing pathway. (Flowchart-step14)

During early development (probably before age 3 years), this may lead to excessive flow of information from sensory areas to the higher integration areas such as association cortices and prefrontal lobe which may cause prematurely accelerated growth of these higher order brain areas as truly observed in autism. This would be the reason of why autistic children have certain unusual talents and older autistics are excellent on task involving long term memory like recall of train time-tables, historical dates, chemical equations or recall of the exact words of songs heard years before (Carper et al., 2002)

Ultimately the hyper-preference processing in the sensory domain, may lead to exaggerated selectivity, sensitivity and specialization of simple sensory features. As a consequence-
Autistic children would remain with fragmented and amplified perception of bits and pieces of the world.

Autistics may have abnormal and obsessive attention to detail and hence can notice the smallest change in their environment.

Autistics may become hyper-focused in arbitrary subjects of interests and sustain their attention on these subjects for unusually long time periods.

On the whole, this hyper-connectivity phenomenon may cause for enhanced perception of sensory fragments; focus on details and deficit in complex and more holistic processing.

- As per the Ayurvedic aspect, pranavayu promotes and regulates the other biophysical components and sense faculties (by the virtue of prerana karma) to perform their respective functions (Chaturvedi G. & Shastry K., 1996). But as described earlier, vitiated prana vayu may unable to perform its function of synaptic connectivity properly and so as to fail to regulate the functions of other components, rather consequently responsible for impairment of manas, buddhi and other doshas. (Flowchart-step7,8)

- Due to impaired manas, the functions related to motor control, abstract thinking and thoughtful planning may upset and lead to non-oriented information processing (Chaturvedi G. & Shastry K., 1996) (Flowchart-step9).

- Due to impaired buddhi, particularly dhriti, the function of selective attention and further retention may disturb leading to excessive storage of primary information (Chaturvedi G. & Shastry K., 1996) (Flowchart-step10).

- Functions of sadhak pitta simply resemble with the functions of neocortex and amygdala. As cognitive functions represented by sadhak pitta can be represented in the form of buddhi and medha (Arunadutta, 2002) as well as function of emotional & social cues are represented as bhaya, shaurya (Chaturvedi G. & Shastry K., 1996) etc. But due to derangement of sadhak pitta, the exaggerated processing of sensory, cognitive and emotional cues take place thereby leading to overflow of primary knowledge (Flowchart-step11, 12).

- Memorization i.e. smriti is a function carried out by udan vayu (Arunadutta, 2002). But due to its derangement and hyper preferential mnemonic pathway, autistic child may show excessive retrieval of working memory as well as long term memory of only primary features (Flowchart-step13). But in older autistics, working memory functions are seen widely upset, although long term memory may remain intact due to repetitive maintenance rehearsal. This may be suggestive of ongoing degradation of Udan vayu due to local background pathology (Flowchart-step14).

- Concept of hyper-memory can also be explained with the help of an Ayurvedic principle i.e. ‘Samanyam Vridhikaranam’ (Chaturvedi G. & Shastry K., 1996). According to this theory, generic concomitance may augment the same class of characters, in turn may responsible for their overloading.

- Such an overspecialized hyper-memory may tend to activate even by the mild environmental stimuli of same class of knowledge and further integrate with its processing to develop hyper-preferential pathway. This mechanism is also supported by one of smriti-hetu (Factors responsible for memory) i.e. ‘sadrishyat smritirupajayate’ (i.e. similarity between current knowledge and previous experience). (Chaturvedi G. & Shastry K., 1996) (Flowchart-step14).

Back on continuing modern pathophysiology of autism, in general, it is observed that the autistic children may seem normal, rather, gifted at the initial period of development, the symptomatology of autism
initiates after the age of 18 months or before the age of 3 years when child begins to learn more complex task. The symptomatology may be driven by under-connectivity of long range of connections required for complex task.

B. Under-connectivity to long range complex sensory pathway

As described earlier, long range neuronal connections play a key role in complex information processing (Minshew & Goldstein, 1993). But in autistic brain, under-connectivity may observed between long range columns of different brain regions. Hence there is an increasing impairment in integrating progressively more complex information across different brain regions which in turn results into memory deficits for complex and abstract material (Flowchart - step15).

Also the background mechanism of hyper-preferential sensory-mnemonic pathway of short-range columns, also inhibit the higher order information processing. As on exposure to environmental stimuli for complex task (Flowchart - step16), the hyper-preferential pathway become activate and enhances its sensitivity for selective simple features. This may synergistically processed by the consolidated mnemonic inputs (Hyper-memory) of previous primary information and results into dominance of the earliest features and avoidance of processing of other features. Such hyper-autonomous and overly selective pathway leads to following symptoms with respect to different brain regions (Flowchart - step17).

i. Somatosensory cortex : (Flowchart-step18)

Under-connectivity to long range circuits and hyper-connectivity with microcircuits in neocortex, particularly somatosensory cortex causes exaggerated perception and attention of fragments of sensory world which must be holistically processed at normal circumstances. This may enhance by hyper plasticity component which drives exaggerated memories to further amplify the processing of same stimulus and also drive over generalization of attention to all related forms of the stimulus. Thereby the positive consequences are exceptional capabilities for primary and specific tasks while the negative consequences are impairment of holistic processing and a limited repertoire of behavioral routines, which may further repeated obsessively i.e. stereotyped behavior, a core characteristic of autism (Flowchart -step19).

Similarly in the domains of auditory, visual & touch stimuli, autistic people on positive consequence may exhibit enhanced discrimination capabilities for elementary stimuli and on negative consequence, they may exhibit the diminished global interference for complex stimuli due to impaired pre-pulse inhibition (Foxton et al., 2003 Mottorn et al., 2003). This will lead to hypersensitivity to environmental sound, light and touch stimuli, which is observes as key characteristics of autism (Flowchart - step 20).

- In an Ayurvedic paradigm, stereotyped behavior and hyper-sensitivity to touch, light and sound are the features demonstrated by impaired vyan vayu (Arunadutta, 2002) (Flowchart -step19, 20).

ii. Prefrontal Cortex: (Flowchart -step21)

Downside of hyper-connectivity and under connectivity of cognitive regions, particularly PFC, indicates impairment in higher executive functions. Excessive memory in low level sensory and elementary cognitive regions may lead to an early over-specialization of primary feature processing, missed developmental opportunities to acquire a full spectrum of primary processing strategies and to build higher order strategies. This might lead to a fragmented alphabet of feature processing capabilities in the vocabulary of sensory processing and obstruct the development of higher cognitive functions such as abstract thinking and language processing. Thus, this mechanism is responsible for language and speech impairment, which is a characteristic of autism (Flowchart -step22).

- In an Ayurvedic paradigm, derangement of udan vayu is responsible for speech impairment (Arunadutta, 2002).
iii. Amygdala:

In autism the functional impairment of amygdala is resulted into storage of aversive emotional and fear related memories (Flowchart- step23). Later on, exposure to fear stimuli, this preformed memories may lead to progressive generalization of fear which may consequence into behavior and may account for inappropriate reactions to the environment, sudden & inexplicable anxiety attacks, loss of fitness required for social interaction and phobias. These are also core characteristics of autism. (Flowchart-step24)

Impairment in social interactions & communication are other characteristics of autism, i.e. which are also mediated by insufficient activation of amygdala (Pierce et al., 2001). Due to hypo-activation of amygdala, autistic people may become severely unable to “read other people minds” (Flowchart-step25) and empathizing with other people by affecting the following two elements-

✓ Ability to distinguish between oneself and others and realize that other people have independent minds and may pursue different goals from one-self.
✓ The ability to express an appropriate emotional reaction to the other person’s mental state, thus to be unable to empathize with others mind.

On the whole, the deficits in language & speech, undue fear & social phobia, and inability to read other people's mind may altogether mediate impairment in social interaction and communication. (Flowchart-step26)

- In Ayurvedic paradigms the features of emotionality is connoted by Sadhak pitta (Chaturvedi G. & Shastry K., 1996) i.e. bhaya harsha, prasad, krodha, etc. Thus vitiated sadhak pitta may responsible for increased fear and anxiety which lead to social withdrawal and avoidance.

iv. Fusiform face area (FFA):

Eye contact and watching the facial expressions are one of the first signs of cognitively healthy infants and serve to build the basis for successful navigation through a social environment. But deviant eye gaze is a core characteristic observed in autistic child. This is driven by the impaired cortical region, named as fusiform face area. As suggested by its name, in normal subjects this area is highly reactive to face recognition. But in autistic children, fusiform face area is observed to be hypo-reactive which lead to abnormal face perception and social avoidance. (Kanwisher et al., 2000) (Flowchart-step27)

Due to hypo-reactivity of FFA, amygdala may have to confront to response the face and eye recognition stimuli. On exposure, the right amygdala shows greater activation when viewing familiar and unfamiliar faces while left amygdala and left orbito-frontal cortex shows greater activation on viewing emotional faces. Both areas forms part of the emotion circuit of the brain and shows heightened emotional response to these stimuli. Amygdala, simultaneously also makes quick and powerful fear associations with fearful mnemonic-inputs. In consequence to this, Autistic child may spend less time fixating with the eye region resulting into avoidance of eye contact which is a characteristic of autism (Dalton et al., 2005) (Flowchart-Step28 )

- In an Ayurvedic paradigm, eye movement is a function of vyān vāyu. So deviant eye gaze may also the result of deranged vyān vāyu (Arunadutta, 2002).
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**CONCLUSION**

Etiopathogenesis of autism may predominantly evolve from *khavaigunya* as consequence of various *sahaja* (genetic) & *agantuja* (Epigenetic toxic insults & post natal environmental factor) *hetus*. Vitiated *doshas* (physical & mental) may exacerbate the *khavaigunya* leading to various core features of autism. Hyperconnectivity & underconnectivity among short range & long range neuronal pathways respectively may evolve from impairment of *pranavayu* which in turn causes for hyper-perception, hyper-attention & hyper-memory (i.e. impairment of functions of *manas* & *buddhi*). Impairment of *vyana vayu* may...
responsible for stereotyped repetitive behavior, hypersensitivity to light, touch & sound and lack of eye communication. Deranged Udanvayu may result into echolalia and language impairment while deranged Sadhak pitta may cause fear, anxiety and phobia. These features, ultimately contribute to lack of communication & social impairment. On the whole, this Ayurvedic framing of etiopathogenesis of autism may help to understand the contribution of pathological markers in developing symptoms of disease. This knowledge can be further used in Ayurvedic management of autism by reducing the effect of ‘khavaigunya’ through restoring the functions of other pathological markers and normalizing the functions of manas, buddhi (with dhee, dhriti and smriti), vitiated doshas and trigunas, which in turn, may helpful in reducing problematic behavior that would be adaptive at lower rates as well as maintaining this adaptive behavior for longer duration. In addition, it may help in acquiring new skills of leaning and communicating.

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