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Autism; An Approach for Definite Etiology and Definitive Etiologic Management

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Abstract The study aimed to demonstrate a correlation between the challenge of ***Helicobacter pylori*** prevalence and the challenging spread of autistic behavioral disorder. Autism constitutes a challenging unsolved puzzle affecting disadvantaged children at early age where they grow normal until age of 18-24 months then they begin failure to develop some skills or loose already developed skills. The exact etiology of the condition remains unclear while all promises of complete cure are unsuccessful. The association of gastro-intestinal (GI) troubles with autism is frank and the importance of early life gut microbiota in shaping future health was always considered. Disturbances of the structure of microbiota by chronic antibiotic exposure could affect physiology and behavior therefore, strategies of probiotic supplements were suggested to improve GI symptoms and brain functions in autism. ***H. pylori*** was suggested as one of the environmental reasons that could be directly related to many medical challenges. ***H. pylori*** could get forced to migrate to the colon under the influence of antibiotic violence leading to accumulation of excess amounts of ammonia. The accumulated ***H. pylori***-produced ammonia conforms with the observation of elevated serum ammonia among autistic children and its toxic effect with the hypothesis of the entire brain compromise suggested to explain inability of autistic children to perform complex interactions. Ammonia could trigger its toxic effect early on fetal brain due to elevated serum ammonia of ***H. pylori***-dyspeptic pregnant ladies. Interestingly, kids develop the abnormal colonic ***H. pylori*** strains trans-familial at an early age which is the typical timing where children start to develop autistic features or loose already developed skills. The study included 19 children with an average age of 36 months, 16 boys and 3 girls seen at different onset, only one boy two years old was seen at very early onset of the disease. Children and parents were investigated for existence of colonic ***H. pylori*** using a specific test and serum ammonia level was tested for children. Colon care and colon clear with the natural senna purge and vinegar therapy were employed for them. All children and their parents were found positive for colonic ***H. pylori*** strains, and serum ammonia was elevated in all children, they became free of colonic ***H. pylori*** strains after colon clear. All children showed different degrees of improvement but none of them was cured except the boy seen at the early onset of the disease who recovered completely. On conclusion, autism might not be a disease of definitive cure because of permanent compromise of some areas of the brain but it could be a disease of definite prevention.

Keywords Autism, Autism spectrum disorder, Helicobacter pylori, Senna, Vinegar

1. Introduction

Autism is a brain disorder that limits a person's ability to communicate, correlate and relate to other people. It is a series of neuro-developmental disorders that are characterized by deficits in both social and cognitive functions [1]. It first appears in young children, who fall along a spectrum from mild to severe presentation. Some people can navigate their life; some have exceptional abilities while others struggle to speak. Autism spectrum disorders (ASD) affect about one child in 68, striking nearly five times as many boys as girls [2, 3]. It was concluded that genetic and environmental factors are both responsible for the etiology of ASD. Although epidemiological studies have been conducted to clarify these factors but this conclusion remains unclear [4, 5].

Before turning three, careful observers can discover development of signs of autism in a child. Some children develop normally until 18-24 months of age and then they stop or loose previously acquired skills. Signs of development of ASD could include repeated motions (rocking or spinning), avoiding eye contact or physical touch, delay in learning to talk, repeating words or phrases and getting upset by minor changes [5, 6].

Young infants are very social even in the first year of age therefore; it is possible to detect early signs of autism as early as how babies interact with their world. At this age, a child

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with an ASD may not turn to a mother's voice, respond to his own name, look people in the eye, have no babbling or pointing and no smiling or responding to social cues from others [7-9].

The signs of autism are more noticeable in a child's second year., other children are forming their first words and pointing to things they want, a child with autism remains detached showing no single words at age of 16 months, no pretend games at age of 18 months, no two-word phrases at age of 2 years, loss of language skills, no interest when adults point out objects, such as a plane flying overhead [6, 7].

Children with autism may sometimes have physical symptoms including digestive troubles such as constipation and sleep problems. Children may have poor coordination of the large muscles used for running and climbing or the smaller muscles of the hand. Children with autism could also have seizures [4, 10].

It was long believed that autism affects only those regions of the brain that control social interaction, communication and reasoning; instead it is suggested that the disorder in autism affects the entire brain. It was found that even highly functioning autistic children are having difficulty when asked to perform a wide range of complex tasks involving other areas of the brain. It was suggested that different parts of the autistic brain have difficulty working together to process complex information; this may be the driving component of autism [11-17]. These findings could indicate that a further understanding of autism will not likely come from the study of factors affecting one brain area or system but from the study of factors affecting many systems of the brain. The earlier diagnostic assessment of autism in children and adults was based on three main behaviors; they typically have problems with social interactions, verbal and nonverbal communications. They tend to exhibit repetitive behaviors or narrow obsessive interests. It is increasingly clear that other areas of brain function are affected as well, including balance, movement and memory [18-25].

It was reported that autistic adults are having difficulty performing certain complex tasks that involve different areas of the brain working together; this could offer further evidence to support the whole-brain hypothesis in autism. In an effort to confirm the findings of autism, highly-functioning autistic children were compared to non-autistic children with similar IQ, ages and all could speak, read and write. It was found that autistic children did as well as or even better than non-autistic children when asked to perform basic tasks but they scored much less when asked to perform complex tasks [16, 18, 22, 25]. The better the understanding about autism and the brain, the better effective and efficient therapy could be designed. Accordingly, the whole-brain disorder hypothesis in autism could allow new treatment approach for fundamental cure of autism particularly when sufficient opportunity for cognitive growth and development rehabilitation are allowed.

A permanent pathologic sequels involving different areas of the brain which have possibly influenced brain development early during fetal life have been demonstrated by different reports such as specific alterations in white matter structural property [26, 27]. Abnormalities of specific components of grey matter structure in early brain growth patterns of autistic children have been reported by some investigators. Children with more autistic traits showed widespread areas of decreased gyrification [14, 15]. White matter impairment, dysplasia with abnormal cortical thinning or decreased cortical thickness have been identified among children with autism [22-24, 26].

Most investigators were successful to come in agreement that various gastro-intestinal (GI) factors may contribute to behavior in children with autism [1, 4], but they mostly missed to successfully achieve the real pathology behind these GI factors in contribution to autistic behavior. The last three decades have demonstrated prevalence of abnormal-behavior ***Helicobacter pylori*** strains and the flare up of a lot of medical challenges related to these ***H. pylori*** strains via inflammatory, toxic, immune or different unknown reasons to the extent that the medical world has believed that ***H. pylori*** eradication should be a necessary attempt [28, 29]. Accordingly, a research motive for this study has developed with purpose to investigate for a possible correlation or contribution of ***H. pylori*** dyspepsia in leading to ASD among disadvantaged children.

2. Aim

Demonstration of a possible relationship between ***H. pylori*** and the GI symptoms associated with autism in leading to an impact on the entire brain with purpose to find out an etiologic pathology and definite cure.

3. Design & Setting

A multiple-case clinical study which was done in Jeddah/Saudi Arabia during the period May 2014 to October 2015. The protocol of the study was approved and the study followed the research committee ethics.

4. Patients & Methods

The study started with 25 patients while only 19 continued the follow up as most parents of autistic children had lost confidence in possibility of cure. Autistic patients are not identical in symptomatology as they markedly vary in type, grade of symptoms and susceptibility for developing the disease. Hence; the study included 19 autistic children with variable symptoms and different grades of the disease. They were 16 boys and 3 girls, their age ranged between 11 months and 6 years with an average age of 36 months. The study included one boy 2 years old who was seen at a very early onset of the disease; few days of losing the developed skills and included an 11 months girl with typical autistic features but atypical early age of developing autism.

Existence of ***H. pylori*** in the colon was tested for children

and parents by employing specific test (***H. pylori*** fecal antigen test) [28, 29]. Serum ammonia level was tested for all children. ***H. pylori*** fecal antigen test was obtained from Acon Laboratory, USA.

Natural ***H. pylori*** eradication from the colon was done employing the senna leaves purge and intake of vinegar-mixed salad once or twice daily for children and parents [29].

5. Results

All children and parents were found positive for colonic ***H. pylori*** strains; they became free of ***H. pylori*** strains in the colon after the natural therapy as confirmed by ***H. pylori*** fecal antigen test and serum ammonia was found elevated in all children. The level of serum ammonia was found ranging between 99-113 umol/L except the boy with newly-discovered onset of the disease who has got a serum ammonia level of 351 umol/L and the eleven-months girl who has got a serum ammonia level of 279 umol/L. The normal reference of ammonia level of this study was 18-72 umol/L for all ages.

All children showed different grades of improvement but none of them was cured after six month of therapy and further six months of follow up except the child seen at a very early onset of the disease who recovered completely. The eleven-momths girl who developed autistic features at early age (7 months) was suggested to develop drastic ***H. pylori*** strains from her mother; therefore, ***H. pylori*** DNA extraction in the stool was done for the girl and parents. This girl also markedly improved but was not completely cured.

Revision of previous records of serum ammonia done one year earlier to this study for a group of 16 non-autistic children studied for their low IQ scores who were free of abdominal symptoms and colonic ***H. pylori*** strains, serum ammonia level was found ranging between 49-57 umol/L. Further revision of the records of a group of 21 children with 2-5 years autistic history who were positive for colonic ***H. pylori*** strains with an age range of 4-7 years studied during the same period of this study in order to demonstrate the effect of the senna purge in clearance of the elevated serum ammonia. Their serum ammonia level ranged between 90-107 umol/L. Colon clear was done for them and the serum ammonia level dropped on next 2 days to a range of 32-41 umol/L.

6. Ethical Considerations

An informed signed consent was taken from all parents; children were allowed to lead their routine style of life except strict follow up of dietary instruction of colon care and extreme restriction of outside-home food intake. Parents were free to make their children quit the study at any time whenever they feel inconvenience towards the natural therapy or strategy of the study.

7. Discussion

Although various reports in literature refer with great concern to the role played by ***H. pylori*** in disease pathology [28, 29], research studies seldom indicated directly to the possibility that ***H. pylori*** could stand behind the pathogenesis of Autism. Recent clinical studies have revealed a high prevalence of GI symptoms such as inflammation and dysfunction in children with autism. Mild to moderate degrees of inflammation were found in both the upper and lower intestinal tract and decreased digestive enzyme activities were reported in many autistic children. Treatment of digestive problems appeared to have positive effects on autistic behavior; these new observations represent only a piece of the unsolved puzzle "autism" and should stimulate more researches into the brain-gut connection [30].

As ASD is often associated with different GI disturbances which may also impact behavior; therefore, alterations in autonomic nervous system functions should be also expected frequently in ASD. The relationship between these findings in autism is not clearly known. It was suggested that autonomic functions and GI problems are intertwined in children with ASD [31]. Although the exact etiology and pathology of ASD remain unclear, a disorder of the microbiota-gut-brain axis is emerging as a prominent factor in the generation of autistic behavioral disorders. Clinical studies have shown that GI symptoms and compositional changes in gut microbiota frequently accompany cerebral disorders in patients with ASD. A disturbance in the gut microbiota which is usually induced by a bacterial infection or chronic antibiotic exposure has been implicated as a potential contributor to ASD. The bi-directional microbiota-gut-brain axis was suggested to be acting mainly through neuro-endocrine, neuro-immune, and autonomic nervous mechanisms. It was reported that application of modulators of the microbiota-gut-brain axis such as probiotics and certain special diets might be a promising strategy for the treatment of ASD. Different observations of disruption of the microbiota-gut-brain axis as concerns the pathogenesis of ASD has therefore suggested its potential therapeutic role in autistic deficits [1].

A gut to brain interaction in ASD and the role of probiotics on clinical, biochemical and neuro-physiological parameters in autistic individuals have been emphasized and confirmed in further reports. It was adequately reported that the high prevalence of the frequent GI disturbances in patients with autism might be linked to gut dysbiosis representing a phenotype of a "gut-brain axis" disruption. Employment of strategies that can restore normal gut microbiota and reduce the gut production and absorption of toxins such as probiotic supplements in diet may represent a non-pharmacological option in the treatment of GI disturbances in ASD. The effect of probiotic supplements in autistic children is not only specific on GI symptoms but also to improve the core deficits of the brain disorder, cognitive and language development, brain function and connectivity [32]. It was further reported

that specific assessment of gut functions including the microbiome would be necessary to evaluate the contribution of gut physiology to functional constipation observed in autistic children [33]. As much as GI symptoms were frequently reported among autistic children; an impact of GI co-morbidity on ASD behavioral problems has been hypothesized. 'Constipated' and 'Not-Eat' were described as the most frequent GI symptoms in autistic individuals [34]. Alteration in intestinal function which was often referred to as a "leaky gut" due to mucosal inflammation has been attributed to children who are on the autism spectrum; this particular symptom was even put into consideration to identify children with autism who have atypical symptoms [35].

The concept of gut-brain axis, its regulation by the microbiota and its role in the biological and physiological basis of neuro-developmental and neuro-degenerative disorders could constitute a considerable role in the pathogenesis of autism. The importance of early life gut microbiota in shaping future health outcomes should be also considered. Disturbances of this composition by way of antibiotic exposure can result in long-term effects on physiology and behavior [21, 36]. ***H. pylori*** in the stomach is leading the behavior of natural bacteria as it does not exist in the gastric lumen during presence of food and it remains settling juxta-mucosal under the mucus layer of gastric mucosa with the ammonia at its immediate vicinity functioning to protect the gastric wall from its acid if it goes in excess [28, 29]. Therefore; the antibiotic violence towards ***H. pylori*** forcing it to migrate to the colon could definitely disturb its natural microbiotic function with its expected sequels on human body physiology.

The routes of communication between the microbiota and brain are being unraveled and could include the microbial metabolites such as ammonia [21, 28]. As ***H. pylori*** could migrate or get forced to migrate to the colon under the influence of antibiotics, it will continue producing ammonia for a reason or no reason, unopposed or buffered by any acidity, leading to accumulation of profuse toxic amounts of ammonia. Colonic ***H. pylori*** strains in their abnormal colonic habitat could lead to adverse toxic effects in the body; certainly the delicate physical structure of a child during early growth could be also severely affected by these aggressive drastic strains and the delicate integrity of the child's growing brain could be further in susceptible children a fragile target to the toxic influence of colonic ammonia [28, 29, 37, 38].

The hypothesis of the entire brain involvement in autism was designed on the basis of impairment of the histology of whole areas of the brain in order to explain inability of autistic children to perform complex tasks [11, 13-17, 21-23]. In spite of the finding that many investigators have demonstrated rise of serum ammonia level among autistic children, they missed to indicate the possibility that elevated levels of serum ammonia could influence the entire functions of the whole brain [39-49]. Serum level of ammonia was also found elevated among all children in this study.

H. pylori colonized the stomach since an immemorial time as if both the stomach and the bacterium used to live together in peace harmless to each other and hence ***H. pylori*** has been considered by some investigators a natural bacterium [28, 29]. ***H. pylori*** when forced to migrate to the colon, mainly under the influence of antibiotic violence, will lead to different dyspeptic symptoms and accumulation of profuse amounts of ammonia in the colon with consequent elevated levels of serum ammonia [28, 29, 50, 51]. It is common that ladies develop dyspepsia during pregnancy; abnormal ***H. pylori*** strains are responsible for most cases of functional dyspepsia, but it is rarely recognized that this dyspepsia is ***H. pylori***-related [52]. Accordingly; serum ammonia would be elevated in both maternal blood of those dyspeptic pregnant ladies and in the fetal blood in turn with the possibility of a toxic influence of ammonia on the delicate structure of the developing fetal brain leading also to sensitization of the fetal brain during early embryonic life to the adverse effect of ammonia. It has been reported that the neuropathy in autism starts early during embryonic life due to heterogeneity [11, 27, 53]. The sustained elevated ammonia level in fetal blood caused by the colonic ***H. pylori*** strains of dyspeptic pregnant mothers could constitute a trigger of a causative pathology for neuro-development of autistic disorders confirming accordingly with the suggestion that both environmental and genetic factors are responsible for the etiology of autism [4, 5].

The suggestion that the elevated residual ammonia serum level in fetal blood plays an early causative pathogenic factor in leading to the autistic neuro-developmental disorders since embryonic life conforms with an observational finding in this study expressed by mothers of 7 autistic children during their delivery. The mothers confirmed a frank history of ***H. pylori***-related dyspepsia during their pregnancy which had been confirmed by specific laboratory tests, they were just able to follow gastric sedatives. They were astonished that their babies did not cry immediately after delivery and suction of their secretions in spite of their good general condition. Those mothers continued to have ***H. pylori*** dyspepsia after delivery because of a contraindication for eradication therapy or failure of therapies as antibiotics are seldom effective against extra-gastric ***H. pylori*** strains [28, 29, 54]. Later, their kids developed autism between the age of 2-3 years.

Existence of ***H. pylori*** in children occurs trans-familial via food at an early age; this matter is confirmed by the fact that ***H. pylori*** strain of children is often identical with that of their parents. Interestingly, children maintain the same strain genotype life-long even after moving to a different environment unless eradicated. ***H. pylori*** travels between parents via oral to oral route while transmission to kids occurs via meals [37, 38]. The kids develop the abnormal-behavior colonic ***H. pylori*** strains at the time of their weaning when they start to share the dining table with their parents; that is typically the critical timing where children begin to develop autistic features or loose already developed skills [5, 6, 28, 29].

Migration of ***H. pylori*** to the colon occurs mainly under the influence of antibiotic exposure. Existence of ***H. pylori*** in the colon is typically life-long unless eradicated as antibiotics are seldom effective against extra-gastric ***H. pylori*** strains and no available measure has been proved to effectively eradicate ***H. pylori*** from the colon except the senna purge [28, 29, 54-56]. Accordingly; pregnant ladies who develop abnormal colonic ***H. pylori*** strains via an outside-home query meal would mostly remain dyspeptic and would become later in most instances the mothers of autistic children due to recurrence of a causative pathology which has triggered its effect during pregnancy and made the fetal brain already sensitive to the toxicity of ammonia earlier throughout the embryonic life.

As concerns revision of literature knowledge regarding existence of ***H. pylori*** in children, It is now recognized that ***H. pylori*** like most enteric infections is mainly acquired during childhood. The age at which children are most likely to become infected is still unclear but findings in a number of cross-sectional studies suggested that infection is acquired before the age of five [57]. Other studies suggested an earlier age before two years via trans-familial transmission from parents which is the time of weaning and it is at the same time the typical timing of developing autism [28, 58]. Existence of ***H. pylori*** in children is community-related (less in developed and more in developing countries) and it has got a clear age-related prevalence; that is increasing with age [59]. All figures differ with life style changes, dependency on fast food meals and migration of food handlers from poor to rich countries. Children can contract ***H. pylori*** through poor hygiene, child care, or living with another person who has the bacteria. ***H. pylori*** is a common bacterium found in the stomach of many children. In fact, some studies suggest that up to 50 percent of the world's population carries this bacteria. Children develop ***H. pylori*** by fecal-oral, gastric-oral, or oral-oral route. Risk factors for infection include poor socio-economic status, child care, close living quarters, poor hygiene and living with another person who has ***H. pylori***. Asian Americans and African Americans get infected at about the same rate as children in developing countries [58, 60]. The prevalence of infection is highest in children in the developing world where up to 75% of children may be infected by the age of 10, while in the developed world the prevalence of infection is noticeably increased among socially deprived children [57].

Concerning prevalence of ***H. pylori*** among autistic children and their parents, it is worthy to mention that there is no available knowledge in literature about prevalence of ***H. pylori*** among children with autism; this might be a good point in favor of the value of this study as it might in this regard open a new field of study for researchers and investigators.

In addition to the toxic influence of ammonia, excess amounts of ammonia in the colon is smooth muscle spastic leading to multiple colonic spasms and a high rectal spasm which were demonstrated in ***H. pylori***-dyspeptic adults by colononoscopy. These spasms interfere with the integral colonic function of forming the motion contents, instead it squeezes the colonic contents leading to constipation and formation of small pieces of dried stool [50]. Existence of ***H. pylori*** in the colon was confirmed by a specific test (***H. pylori*** fecal antigen) which was found positive in all children and parents of this study. Constipation and passage of small pieces of dried stool are cardinal signs of colonic ***H. pylori***-related dyspepsia [50, 51]; these signs were found constant features in all children of the study.

The constant association of GI symptoms with autism to the extent that gluten-free diet and probiotics were employed to improve these symptoms could further support the possibility of the role of ***H. pylori*** behind pathogenesis of autism disorder. It has been furthermore suggested that strategies of probiotic supplements that can help to restore normal gut microbiota and reduce the gut production and absorption of toxins has been advised and employed not only to improve GI symptoms in autism, but also to improve the core deficits of the brain disorder [32]. The mucosal pathologic behavior of ***H. pylori*** abnormal strains includes apparent lymphoctic infiltration and lymphocytic mucosal inflammation [61]; small bowel enteropathy has been reported in literature among patients with autism that could be attributed to embedding of ***H. pylori*** colonization towards small intestinal mucosa which is a further unrecognized unusual behavior of ***H. pylori***. [28, 29, 62] GI symptoms were frank and constant among patients of this study; minute-size continuous intestinal sounds were diffusely audible over the center of abdomen that had been related to small intestinal irritation. Small intestinal enteropathy could account for the observations of "No Appetite", "No Hunger" and "No Eat" symptoms among autistic children of the study as they would feel continuous abdominal discomfort. It was suggested that autonomic functions and GI problems in autistic children are linked together [31]; therefore, the quite passive peaceful attitude of some autistic children; "Non-Smiling", "Non-Reactive" was attributed in this study to a degree of parasympathetic activation caused by the minor dull somatic intestinal insult. The improvement of intestinal symptoms among children of this study upon intake of a warm mint drink, a soft caffeine drink or chocolate was attributed to improvement of this autonomic compromise. Constipation, weak appetite, passage of small pieces of dried stool or leaking small amount of soft retained/overflowing stool were encountered as constant features among children of this study.

Major colonization of abnormal-behavior ***H. pylori*** strains is necessary to induce symptoms and toxic complications. Spontaneous reduction below the pathologic level (50%) or even spontaneous elimination of ***H. pylori*** from the colon could occur due to variable reasons such as diarrhea or intake of foods containing bio-organic acid [28, 29, 63]. This could explain the wide variation in autistic features and the observation that some children develop some autistic symptoms then they skip the disease as they grow up.

This study included two children newly diagnosed for autism, one is two years old who started pronouncing some

words and then he lost this skill. Immediate colon clear was employed for him and his parents within few days the clinical diagnosis was made up, that was followed by complete recovery of the child's skills. The other was three years old when diagnosed but he had lost the developed verbal skills one year earlier; he improved but did not recover completely after colon clear. The study also included a girl 11 months old; it is surprising to find a baby of that age who does not cry or even smile in response to her mother's plea, she was looking constantly to one direction and was never responsive or attentive towards her mother's voice. She was typically constipated and was crying only during passing the motion in the form of small pieces of dried hard stool. The father was having frank constipation and severe colonic dyspeptic symptoms due to frequent outside-home meals during his business lunch and dinner meetings. ***H. pylori*** fecal antigen test was strongly positive for the girl and the parents; definitely the bacteria travelled from husband to his wife who gave it to her kid possibly while preparing and tasting her feeds or kissing her baby on the lips. Unfortunately, this girl was seen few months after she developed these features; immediate colon clear with a calculated dose (45 CCs) of the senna leaves extract purge was employed for her followed by vinegar-mixed fruit yoghurt twice daily. The girl improved within few days but did not recover completely because of late discovery and management of her condition; her motion became easy without tragedy, the girl started to smile, look towards her mother, respond to her mother's voice and most importantly she learned to cry like any baby of her age when neglected for some time. ***H. pylori*** DNA extraction in the stool and ***H. pylori*** strain genotyping were done for the girl and parents; they were found having the same strain genotype with existence of cytotoxin-associated gene A (cagA) positive ***H. pylori*** strains. It was emphasized that cagA of ***H. pylori*** encodes a highly immunogenic and virulence-associated protein; the presence of this virulent gene in the body could affect the clinical out-come in many children [64].

All living organisms produce ammonia as a byproduct of cellular metabolism, ammonia is the major end product of cellular amino acid metabolism. Ammonia is a highly toxic material in animals at even sub-millimolar concentrations. At high concentrations, ammonia is toxic and can cause adverse effects to the cell. Effects include disruption of cellular energy metabolism, mitochondrial dysfunction, modulation of inflammatory responses and neurotransmission in neurons. Existing evidences suggest that accumulation of ammonia in the brain affects neuronal function and may lead to several neurological abnormalities [65-69]. In mammalian brains, ammonia is derived mostly from protein metabolism. In the brain, ammonia is derived from two main pathways; endogenous and exogenous sources. Endogenous sources of brain ammonia involve hydrolysis of proteins and degradation of amino acids [70-72]. Exogenous sources produce large quantities of ammonia in the gastrointestinal tract resulting from bacterial splitting of urea and deamination of amino acids. Bacterial infections in the gut are major causes of accumulation of ammonia in the brain [68, 73]. In addition to the fact that ammonia can diffuse blood-brain barriers (BBB) due to its small size and uncharged state leading to major toxic damage in the brain, elevated ammonia also could dissociate changes in BBB morphology and permeability allowing other toxins to diffuse with all expected bad sequels [68, 74, 75]. It was shown in individuals with hepatic encephalopathy that there is lack of balance between excitatory and inhibitory neurotransmission [76].

In rat brain it has been shown that high ammonia concentrations markedly interact with mitochondrial function [77]. In most animal species, including mammals, the ammonia concentration of body fluids is typically low, high concentrations are usually toxic to mammalian cells [69, 78]. In animals, high levels of ammonia can lead to disruption in the balance between mitochondrial fission and fusion, changes in mitochondria morphology, mitochondrial enzymatic failure, disruption of energy metabolism of mitochondria and a reduced rate of mitochondrial axonal transport [79, 80]. The elevation of ammonia concentrations progressively leads to impaired mental status as concerns cognitive, learning, and memory functions. It has been shown that exposure of rat hippocampal slices to high ammonia concentrations compromised the neuro-receptors. It was found that elevated levels of ammonia impairs memory or conditioned learning in animals [81, 82].

In most species, including mammals, ammonia concentrations exceeding 1 mmol/L are usually toxic to mammalian cells. Because of its toxicity an effective ammonia detoxification or excretion system is crucial to maintain cellular and body fluid ammonia levels within a tolerable range to ensure normal systemic functions [68, 83, 84]. In this study, colon clear via employing the natural senna leaves extract purge was the method used for ***H. pylori*** eradication from the colon in order to clear the accumulated colonic ammonia.

Ammonia could have a biphasic effect on cerebral micro-capillary circulation, an early enhance due to endothelial-derived nitric oxide liberation via the effect of shear stress and a late harmful toxic effect. The possible mechanisms of the learning deficits produced by high levels of ammonia most likely involve a reduction of the neuronal glutamate-nitric oxide cyclic pathway [69, 78, 83, 84]. This biphasic influence of ammonia on the cerebral micro-capillary function could account for the brilliant early skills or the high IQ scores of some autistic children which is followed by loss of already developed skills to the extent that the investigators of the study found some parents of autistic children in developing countries believe that an evil eye has affected their children and they search spiritual therapies. Parents are looking everywhere for answers and best treatment even they are trying some traditional therapies including intensive behavioral approaches but with no "one-size-fits-all" treatment approach, parents often turn to diverse complementary and alternative therapies [75]. The investigators of this study noticed that people in some

Middle East countries practice a lot of spiritual traditions and repeated sessions of bee bites therapy as an attempt for recovery of their children.

Permanent compromise of some areas of the brain among autistic children such as impairments of grey or white matter, decreased cortical thickness or cortical thinning leading to dysfunction of complex interactions in disadvantaged children was confirmed in literature [13-15, 22, 24, 26]; possibly for this reason, most researchers were just able to achieve improvement through employing different measures but never complete cure of their autistic patients. The results of this study conform with the literature results in achieving incomplete cure of autistic features which could indicate that autism might not be a disease of definitive cure but it could be a typical disease of definite prevention via restriction of antibiotic use unless seriously indicated, extreme carefulness towards outside-home meals, colon care and colon clear upon developing dyspeptic symptoms. If there is a chance for fundamental cure in autism, it might be via colon care and colon clear for both kids and parents. Early diagnosis and management are precious in this situation; recovery of the developed verbal skills for the two-years old child of this study with the lucky advantage of early discovery of the onset of the disease upon losing the developed verbal words is an ideal example.

Prevention is always far better than treatment; scientific research efforts could not reach until to date an adequate cure of autism, while it could be greatly preventable by protecting children's brain from the bad sequels of the abnormal ***H. pylori*** strains of their dyspeptic mothers. Ladies should be extremely careful towards outside-home meals and strictly avoid un-necessary antibiotic use particularly before pregnancy. On developing any unusual or constant dyspepsia, parents should investigate for existence of colonic ***H. pylori*** strains and eradicate them if present by employing natural measures. Eradication of ***H. pylori*** from the colon can be done via employing the senna leaves purge as no other measure has been proved to be effective against colonic ***H. pylori*** strains; three-times dilution of the natural senna leaves extract was found directly lethal to ***H. pylori*** on culture media. While antibiotics are seldom effective against extra-gastric ***H. pylori*** strains; on the contrary, it will force normal-behavior ***H. pylori*** to migrate to the colon [28, 54, 56]. During pregnancy, employing the senna leaves purge might not be confidently advisable as there is no available evidence against the possibility of development of sudden uterine contractions via a local axon reflex in response to the senna. In this situation, colon care can be employed by having a vinegar-mixed salad with food after any query meal to relief dyspeptic symptoms by buffering bacterial contents of the meal and to reduce colonic ***H. pylori*** strains below its pathologic level [28, 29, 50, 63]. This could protect to a great extent the fetal blood and the embryonic brain from the toxic effect of the ammonia in maternal blood. After delivery, mothers must follow the same strict carefulness and measures particularly during the children's early critical ages of brain growth and development of skills. In addition, mothers should wash hands with white vinegar and water after washing with soap whenever using the bathroom or before preparing food for their children as soap does not kill ***H. pylori*** while 20 times dilution of dietary white vinegar (acetic acid 6%) is directly lethal to ***H. pylori***. [50, 85]

The reason that there are some patients who developed autism before the last three decades which is the particular period of the abnormal-behavior ***H. pylori*** strains prevalence, is most probably due to chronic antibiotic exposure or recurrent antibiotic abuse that would force ***H. pylori*** to migrate to the colon; the suggestion of chronic antibiotic exposure in leading to autistic disorder has been suggested by some investigators.[1] The last three decades demonstrated flare up of abnormal-behavior ***H. pylori*** strains after the rediscovery of a bacterium surviving in the stomach by two Australian physicians and their strategic triple therapeutic violence against it with consequent flare up of medical challenges related to these drastic ***H. pylori*** strains. It might seem that the antibiotic violence has rendered a domestic bug to become wild in sequels instead of getting rid of it. The challenge of autism first appeared before the last three decades but it has mostly dominated during these last three decades [1, 28, 29, 86, 87]. The susceptibility or sensitivity of the brain to the undesired toxic effect of ammonia should differ from one child to another even they are all susceptible disadvantaged individuals; this could explain the apparent variable range of symptoms among autistic patients. It should be considered that those children who develop autism in relation to the toxic influence of the ***H. pylori***-produced ammonia on the growing brain are susceptible predisposed individuals as exposure of some other children to the same circumstances was associated with different sequels such as toxic pancreatitis and development of childhood diabetes [88].

The literature reports indicate increased risk and rising prevalence of identified ASD among U.S. children. An investigator with his 45 collaborators reported in 2009 that the increased prevalence of identified autism among U.S. children need to be regarded as an urgent public health concern [4]. The reason that autism prevails among U.S. children could be most probably related to the fact that U.S. is a typical country of fast food dependency and the food handlers are mostly poor people migrating from poor developing countries with inadequate health care standards carrying with them abnormal-behavior ***H. pylori*** strains; these abnormal strains travel from stomach to stomach via meals and remain in the gut with its abnormal behavior for life unless eradicated [28, 29]. According to some personal communications; some mothers of autistic children indicated frankly that they love fast food to the extent that some particular fast food meals run in their blood while some mothers admitted that they are lazy to cook when they are pregnant and they depend on outside-home meals. Others mentioned that when they get pregnant while the previous baby is still between 2-3 years old, they depend mainly upon fast food delivery for themselves and their kids.

In Summary, realization of the real clue of a challenging illness constitutes the main success in its management; the hypothesis of the pathogenic influence of elevated serum ammonia in leading to the autistic behavioral disorder might remain just a hypothesis until approved or disapproved but the unsolved puzzle of ASD has been considered as a "sequence" rather than a syndrome [23]. Apparently, the current available literature knowledge might seem articulating together to support a concept that the spread of the abnormal-behavior colonic ***H. pylori*** strains could lie behind the pathogenesis of a complex sequence of spectral events leading to the prevailing challenge known as the disorder of autistic spectrum. The following observational findings were considered and discussed in the text: 1. Prevalence of the abnormal-behavior ***H. pylori*** strains followed the antibiotic violence towards it during the last three decades, 2. Flare up of medical challenges related to these ***H. pylori*** strains has started mainly during the last three decades, 3. Autistic behavioral syndrome appeared earlier but dominated during last three decades, 4. Antibiotic exposure was suggested as a factor leading to autistic disorder, 5. The association of GI troubles, that could possibly be ***H. pylori***-related, with autism is frank and constant in literature, 6. Development of autistic features or loss of developed skills occurs at the typical age where children could gain the abnormal ***H. pylori*** strains trans-familial from their parents, 7. ***H. pylori*** in the stomach was suggested to lead a behavior of natural bacteria while the role of microbiota and probiotics in autism is strongly suggested in literature, 8. The elevated serum level of ammonia among autistic children is constant in most scientific reports, 9. The toxic effect of ***H. pylori***-produced ammonia on the whole brain conforms with the hypothesis of entire brain compromise suggested to explain inability of autistic children to perform complex interactions and 10. The concept of ammonia toxicity in autistic sequels can still explain why many children show early brilliance in developing skills followed by loss of these developed skills; ammonia hence is a cure and a poison at same time.

Accordingly, It seems that autism might not be a disease of definitive cure due to a permanent compromise of areas of the brain responsible for development of skills caused by a sustained toxic influence of ammonia throughout a critical period of brain growth during a child's early life. For this reason, scientific research efforts were just able to get improvement of autistic behavioral symptoms but did not achieve real or complete cure of autism. On the other hand, autism could be a typical disease of definite prevention via extreme carefulness towards outside-home meals, restriction of antibiotic use unless seriously indicated and colon care/colon clear for mothers who develop ***H. pylori***-related dyspeptic symptoms before or during pregnancy or while nursing their kid's during the early critical ages of child's growth. Early diagnosis and management of autistic features in a child could greatly improve the out-coming results of treatment through colon clear for the kids themselves.

8. Conclusions

Until today, it seems that this research article may constitute the real fulfilled clue about autism sequences; autism might not be a disease of definitive cure due to permanent compromise of some areas of the brain responsible for development of skills during a critical period of a child's brain growth but it could be a typical disease of definite prevention via colon care and colon clear for parents employing natural measures for any developing ***H. pylori***-related dyspepsia. If there is a chance for cure of autism, it might be via colon clear for kids in an early onset of developing autistic features. In spite of that; this research study invites and encourages all investigators to continue all persevere and enthusiastic efforts to approach a fundamental cure of autism.

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