

## Review Article

# Role of nutritional deficiency in the development of autism spectrum disorders

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## ABSTRACT

Autism spectrum disorders (ASD) are characterized by behavioural abnormalities and impaired communication skills. Both genetic and environmental factors have been attributed as causative factors. It has been reported that there are alterations in the organization of functional networks in brain as well as in the balance between structural and functional networks in brain in children and adolescents with ASD when compared to normal children. Various studies have shown that lower levels of micronutrients like magnesium, selenium, Vitamin A, Vitamin D and Vitamin E, Folic acid and iron are found in children with ASD. This narrative review was undertaken to highlight the role of nutritional deficiency in the development of ASD in children relevant literature was collected from Google scholar, Pubmed, Cross Ref and Scopus. This review also takes into consideration how nutritional deficiency during pregnancy, infancy and childhood can have a role in the development of ASD in children.

**Keywords:** Autism spectrum disorders, Brain function, Diet, Nutritional deficiency, Saudi children

## INTRODUCTION

The actual etiology of autism is still a matter of debate. There is a consensus among researchers that both genetic and environmental factors can contribute to the development of autism. Studies have shown that the risk of autism in the siblings of an autistic child is 3%.<sup>1</sup> Higher rate of autism is seen in monozygotic twins than in dizygotic twins.<sup>2</sup> In autistic patients, 15q region of maternally derived chromosome was found to be affected.<sup>3</sup> Structural and functional abnormalities of the brain have been found to be associated with ASD.<sup>4</sup> Since the developing brain is vulnerable to environmental factors, it is believed that there is a strong association between environmental factors and ASD.

The increased prevalence of autism cannot be explained by any single environmental factor. Nutritional deficiency has been studied among the many environmental factors which can contribute to autism.<sup>5,6</sup> Although there is no definite conclusion regarding the role of nutrition, there is evidence that Vitamin D levels are lower in patients with ASD.<sup>7</sup> Maternal metabolic disorders have been found to be associated with ASD. Some researchers have reported that unbalanced dietary patterns of the mother before conception would increase risk of ASD.<sup>8</sup> Although several prenatal and perinatal factors have been reported as risk factors to autism, there is a paucity of literature regarding maternal dietary patterns before conception, during pregnancy and during lactation period as risk factors for autism. In this review, the role of maternal nutritional deficiency and nutritional

deficiency during infancy and childhood in the development of ASD in children is discussed so that future prospective studies with larger samples can be undertaken to establish the role of nutritional deficiency in the development of autism.

## **METHODS**

A total of 61 research articles were selected out of 100 articles collected about autism, which were related to nutrition and autism. The research articles were selected from Pubmed, Google Scholar, CrossRef and Scopmed. The hypothesis that diet of the mother before conception as well as during pregnancy and the diet of the child during infancy and childhood may have an impact on children who are genetically predisposed to autism is examined in detail in this review.

## **DISCUSSION**

The symptoms of Autism Spectrum Disorder can be evident as early as 4 months after birth or they may appear later in childhood. The main environmental risk factors which are also considered as causative factors for autism include advanced parental age, consanguineous marriage, family income, nutritional status of the mother, maternal medication and complications at birth.<sup>9-14</sup>

### *Nutritional status*

Researchers have reported the possible relationship between nutritional status and autism. Some researchers have considered the maternal diet during pregnancy and diet of children with ASD children as modifiable risk factors for the development or worsening of symptoms of autism.<sup>15</sup> Nevertheless, the studies done on the role of nutrient deficiency in the development of autism are not adequate. Another group of researchers have concluded that micronutrients like vitamins and essential minerals may help in improving the symptoms of autism.<sup>16</sup>

Recent studies have highlighted the role of nutrition in the etiology of ASD as well as in treatment.<sup>17</sup> There is also ample evidence for the belief that if children who have a genetic predisposition are exposed to environmental risk factors in a vulnerable period, it can lead to development of autism.<sup>18</sup> Although ASD is regarded as a life-long condition, a significant minority of children with ASD have recovered from the illness.<sup>19</sup>

Individuals with Autism Spectrum Disorders are known to have altered brain function. Antioxidants, vitamins, minerals, and trace elements are needed for the normal metabolism of neurotrophic factors and neurotransmitters in the brain. The effect of these nutritional factors on genes and proteins concerned with brain development and growth is not well established. It is suggested that any factor which can adversely affect the intrauterine growth of the fetus could lead to genetic alterations in the child.<sup>20</sup>

### *Maternal diet and autism*

Maternal nutrition is extremely important for fetal brain development and nutritional deficiency of the mother is considered as a risk factor for schizophrenia and neural tube defects and other neurodevelopmental disorders.<sup>21-26</sup> Nutritional deficiencies can occur in pregnancy because of the increased demands of the growing fetus which can in turn can affect the brain development.<sup>27</sup> This has led to the hypothesis that maternal nutrition may be a risk factor for ASD as well. A study done on pregnant female rats concluded that the maternal protein malnutrition in rats caused behaviors that resembled ASD symptoms in the offsprings.<sup>28</sup>

Since prenatal phase is considered as a susceptible period, researchers have been giving much attention to the nutritional status of mothers of children with ASD.<sup>29</sup> Even though many researchers have investigated the importance of diet and nutrition in children with ASD, there is a paucity of literature which establishes association between maternal nutrition and ASD in the offspring. The present evidence for the role of maternal supplementation with folic acid, iron and multivitamins to prevent autism spectrum disorder (ASD) in offspring is not convincing.<sup>30</sup>

Fatty acids are essential for brain development and studies done to find the correlation between maternal fatty acid intake and ASD risk showed that very low intake of omega 3 fatty intake posed a significant risk. Maternal fish consumption and its effects on development has also been studied.<sup>31</sup> Although antioxidants, vitamins, minerals, and trace elements are needed for the normal metabolism of neurotrophic factors, their interaction with genes and proteins concerned with brain development and growth is not well established.<sup>32</sup>

### *Maternal folic acid levels and autism*

Conflicting results have been found in a systematic review done to find out the effect of maternal folic acid levels on ASD. Studies have shown that the risk of having a child with a neural tube defect (NTD) has a strong association with early pregnancy red cell folate levels.<sup>33-35</sup> It has been suggested that use of prenatal vitamins may reduce the risk of autism in children with genetically susceptible mothers.<sup>36</sup> However, contradictory results have been reported by other researchers that maternal folate was not associated with autistic traits in the offspring.<sup>37</sup> The ongoing clinical trials with folic acid supplementation may prove whether folic acid supplementation has a protective or adverse role, if any, in the development of ASD.<sup>38</sup>

### *Maternal iron levels and autism*

According to researchers, iron is very essential for early neurodevelopment which is altered in autism spectrum

disorder (ASD). They found that low iron intake along with advanced maternal age and metabolic conditions were associated with a 5-fold increased ASD risk.<sup>39</sup> Maternal iron intake can influence both the iron status of mother as well as the child during brain development. Animal studies concluded that decrease in the availability of iron at different phases of development of the child can cause changes in dopamine neurotransmission.<sup>40-42</sup> Iron deficiency can also affect the enzymatic actions involved in nucleic acid metabolism causing genomic instability during DNA synthesis and even influence the proliferation of cells during development.<sup>43</sup> It has been suggested that maternal iron supplementation can overcome effects of inflammation induced hypoferrremia which interferes with fetal brain development resulting in structural and functional brain defects. Since the human hippocampus is highly susceptible to iron deficiency (ID) during late fetal and early neonatal time period, it can alter cognitive development and affects hippocampal cellular growth and function.<sup>44,45</sup>

#### *Maternal vitamin D levels and autism*

Recently studies have been done to assess the effect of vitamin D in skeletal and non-skeletal health during pregnancy, lactation, development in utero and neonatal development. After birth, since calcium absorption becomes dependent upon calcitriol, it can cause hypocalcemia and rickets. As Vitamin D metabolites have poor penetrance into breast milk, breastfed infants have a high risk.<sup>46</sup>

Since Vitamin D is a neuro-steroid, it's neurotrophic and neuroprotective actions can affect the neurotransmission and synaptic plasticity and its deficiency can lead to the pathophysiological changes in ASD.<sup>47</sup> Therefore, some researchers have suggested that gestational vitamin D substitution may help in the prevention.<sup>48</sup>

#### *Nutritional deficiency in infancy and childhood*

##### *Folic acid deficiency in children and autism*

It has been reported that the transport of folate to the nervous system is decreased in infantile-onset low-functioning autistic children.<sup>49</sup> A study conducted on 29 autistic children to assess the effects of folic acid on methylation cycles and oxidative stress showed improvement in social behavior, cognitive ability and communication leading to the conclusion that the children with ASD could benefit from folic acid supplementation.<sup>50</sup> Another study showed that correction of nutritional deficiencies and administration of high-dose folic acid showed improvement in autism spectrum disorders.<sup>51</sup>

##### *Iron deficiency in children and autism*

Though studies have shown that children with ASD have high prevalence of iron deficiency, the number of studies

is limited.<sup>52-54</sup> Hemoglobin levels of children who had severe ASD showed lower values when compared to the children with mild to moderate ASD.<sup>55</sup> Since iron plays an important role in behavioral and motor development some researchers have suggested that iron levels should be measured as a part of routine investigation in autistic children.<sup>56</sup> It is also reported that lower levels of iron may cause changes in serotonergic and dopaminergic systems, cortical networks, and myelination which can affect learning, attention, memory and psychomotor functions and also prevent the acquisition of new skills thus increasing the severity of autistic symptoms in children with ASD.<sup>57,58</sup> More studies should be done to establish the validity of these findings.

#### *Vitamin deficiency in children and autism*

The evidence of gestational and early childhood vitamin D deficiency [25(OH)D <40 ng/ml] causing autism is increasing. Vitamin D regulates about 3% of the 26,000 genes in the coding human genome. Since Vitamin D is a neurosteroid, it helps in brain development by having effects on cellular proliferation, differentiation, calcium signaling, neurotrophic and neuroprotective actions, neurotransmission and synaptic plasticity.<sup>59</sup>

A group of researchers reported that Vitamin D administration showed improvement in the core symptoms of autism probably due to the modulation of neuropeptides such as serotonin and oxytocin which regulate the dysfunctional immunologic process in children with ASD.<sup>60</sup> Our study conducted on 100 Saudi autistic children aged 3-10 years also showed that Vitamin D rich diet may protect the children from developing autism.<sup>61</sup>

## **CONCLUSION**

Since numerous nutrients are needed for the growth and proper functioning of brain in children, maintenance of proper nutritional status may be considered as a key to prevention of autism in children. Since there is a marked improvement of symptoms in autistic children even when a single micronutrient deficiency is corrected, our recommendation is that more studies with larger sample size are needed to find out the role of nutrition, if any, in the prevention of autism.

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