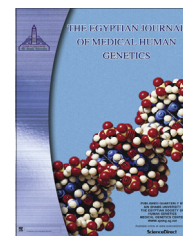




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ORIGINAL ARTICLE

## Study the effect of hyperbaric oxygen therapy in Egyptian autistic children: A clinical trial

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### KEYWORDS

Autism;  
Hyperbaric oxygen therapy;  
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**Abstract** *Background:* Numerous studies of autistic individuals have revealed evidence of cerebral hypoperfusion, neuroinflammation, gastrointestinal inflammation, immune dysregulation, oxidative stress, relative mitochondrial dysfunction, and neurotransmitter abnormalities. Many of these findings have been correlated with core autistic symptoms. For example, cerebral hypoperfusion in autistic children has been correlated with repetitive, self-stimulatory and stereotypical behaviors, and impairments in communication. Specifically, hyperbaric oxygen therapy (HBOT) has been used and can compensate for decreased blood flow by increasing the oxygen content of plasma and body tissues. The aim of this work was to study the effect of hyperbaric oxygen therapy in autistic Egyptian children.

*Patients and methods:* This prospective clinical trial study was conducted on 20 children diagnosed as autism based on DSM-IV-TR criteria (diagnostic and statistical manual of mental disorders, 4th edition criteria, text revised). All patients received at least 20 sessions of hyperbaric oxygen therapy. Sessions were done at pressure 1.5 ATA (atmosphere absolute) with 100% oxygen concentration each lasting for 1–1.5 h either in multiplace chamber or monoplace chamber. MRI Perfusion of the brain was done before and after at least 20 HBOT sessions only for 6 cases.

*Results:* There was a statistically significant increase in the ratio of regional cerebral blood flow (RCBF) to white matter after HBOT in different brain regions when compared to their levels before HBOT.

*Conclusion:* HBOT is a treatment that has recently become quite popular in the autism spectrum disorder (ASD) community. Its benefits cross a wide range of autistic traits as: improved language,

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increased awareness, behavior and socialization by affecting the pathophysiological findings in autism.

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## 1. Introduction

Autism is a neuro-developmental disorder in the category of pervasive developmental disorders, characterized by problems of social communication, inflexible language and behavior, and repetitive sensory-motor movements [1]. Numerous studies of autistic *individuals* have revealed evidence of cerebral hypoperfusion, neuro-inflammation, gastrointestinal inflammation, immune dysregulation, oxidative stress, relative mitochondrial dysfunction, neurotransmitter abnormalities, impaired detoxification of toxins, and impaired production of porphyrins. Many of these findings have been correlated with core autistic symptoms. For example, cerebral hypoperfusion in temporal regions and other brain areas in autistic children has been correlated with repetitive, self-stimulatory and stereotypical behaviors, and impairments in communication [2,3].

Hyperbaric oxygen therapy (HBOT) might be able to improve each of these problems in autistic individuals [4]. Specifically, HBOT has been used and can compensate for decreased blood flow by increasing the oxygen content of plasma and body tissues. HBOT has been reported to possess strong anti-inflammatory properties and has been shown to improve immune function. There is evidence that oxidative stress can be reduced with HBOT through the upregulation of antioxidant enzymes. HBOT can also increase the function and production of mitochondria and improve neurotransmitter abnormalities. In addition, HBOT upregulates enzymes that can help with detoxification problems and impaired production of porphyrins in autistic children which might affect the production of heme, so, HBOT might help to overcome the effects of this problem [5]. HBOT has been shown to mobilize stem cells from the bone marrow to the systemic circulation. Recent studies in humans have shown that stem cells can enter the brain and form new neurons, astrocytes, and microglia. It is expected that amelioration of these underlying pathophysiological problems through the use of HBOT will lead to improvements in autistic symptoms [6]. The aim of this work was to study the effect of hyperbaric oxygen therapy in autistic Egyptian children.

## 2. Patients and methods

This prospective clinical trial study was conducted on twenty children diagnosed as autism based on DSM-IV-TR criteria (diagnostic and statistical manual of mental disorders, 4th edition criteria, text revised) who attended for follow up at the Psychiatry Clinic, Children Hospital, Ain Shams University. The patient's group included 17 males and 3 females, their ages ranged from 2 to 9 years (mean age 5.6, SD  $\pm$ 2.11 years).

Children were allowed to continue all current therapies during HBOT.

All patients were subjected to the following:

- (I) Detailed history taking with special emphasis on: Onset, course, duration of the disease, age, sex of the patient, antenatal, natal, postnatal history, developmental his-

tory (both mental and motor) and accurate details of cognitive abilities and gross and fine motor function, past history and family history concerning similar condition or any psychological or mental disorders. Also history of major childhood illnesses, surgery, injuries, diet, and medication was taken.

- (II) Thorough clinical examination with special emphasis on neurological examination.
- (III) Psychiatric evaluation includes:
  - (1) Confirmation of diagnosis using DSM-IV-TR criteria [7,8].
  - (2) Childhood autism rating scale (CARS) was done before and after at least 20 sessions of HBOT [9].

The scale is used to observe and subjectively rate 15 items. Relationship to people, imitation, emotional response, body use, object use, adaptation to change, visual response, listening response, taste-smell-touch response and use, fear and nervousness, verbal communication, non-verbal communication, activity level, level and consistency of intellectual response and general impressions. Each of the fifteen criteria listed above is rated with a score of Normal for child's age, mildly abnormal, moderately abnormal, and severely abnormal. Total CARS scores range from 15 to 60, score of 30 is considered the cutoff level for a diagnosis of autism on the mild end of the autism spectrum (done before and after at least 20 sessions of hyperbaric oxygen therapy).

- (3) Autism treatment evaluation checklist (ATEC) was done before and after at least 20 sessions of HBOT [10].

The ATEC is a questionnaire that was developed by the Autism Research Institute to evaluate the treatment efficacy in autistic individuals. It consists of four subscales labeled: Speech/Language/Communication, Sociability, Sensory/Cognitive Awareness, and Health/Physical/Behavior. The scores are weighted according to the response and the corresponding subscale. The higher the subscale and total scores, the more impaired the subject [11]. ATEC is used in some studies as an outcome measure [12]. It is designed to allow parents and physicians to assess the outcomes of certain treatments commonly used in autistic individuals. In this study, scores were calculated for the total score and the four separate subscales (done before and after at least 20 sessions of hyperbaric oxygen therapy).

- (IV) Hyperbaric oxygen therapy:

All patients received at least 20 sessions of hyperbaric oxygen therapy (8 patients received 20 sessions, one patient received 30 sessions and 11 patients received 20 sessions followed by another 20 sessions after 2 weeks). Sessions were done at pressure 1.5 ATA (atmosphere absolute) with 100% oxygen concentration, each lasting for 1–1.5 h either in multiplace chamber or monoplace chamber [13].

All children were accompanied during treatment sessions by a parent or adult caregiver. The parents signed a written consent before starting the therapy.

The work has been carried out in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

#### (V) MRI Perfusion of the brain

It was done before and after at least 20 HBOT sessions for 6 cases. MRI perfusion was performed with a 1.5 Tesla signa unit (Philips entera Medical Systems). A multisection T2-weighted gradient echo was applied to obtain axial images. The size of imaging field of view corresponds to (fov) 240 × 240 with head sense coil.

The paramagnetic contrast agent used is Gadolinium DTPA which was injected intravenously (5–10 cc) and injected after obtaining the first three dynamic series while obtaining 37 dynamic series. Five bilateral brain areas (frontal, superior temporal, deep temporal, thalami and prefrontal) were visually assessed. The images were transferred to a work station called extended MRI work station (EWS) for post processing. Regional cerebral blood flow (RCBF) in ml/sec was assessed by scaling the color of the specific area to color scale present in the image given. Ratio of RCBF to the white matter (corona radiata) of the brain at the level of the thalamus is obtained as global differences in RCBF between scans by proportional scaling due to time zone between the pre HBOT MRI perfusion and the post HBOT MRI perfusion as the white matter perfusion is a constant (this is done by comparing the color to the scale in the edge of the image.)

#### 2.1. Statistical methodology

Data are expressed as mean ± SD (range) or as number (%) of cases. Comparison between parameters of ATEC and CARS pre and post HBOT was performed using paired *t* test, the relationship with other parameters was obtained by a Pearson correlation coefficient. Comparison between ratio of RCBF to white matter pre and post therapy was tested by the Wilcoxon Signed Rank Test for six cases only. Analysis was performed by using the Statistical Package for the Social Sciences (SPSS, version 15). The level  $P < 0.05$  was considered the cut-off value for significance.

### 3. Results

This study included 20 Egyptian autistic patients (AD), there were 17 males (85%), and 3 females (15%) with male to female ratio 5.6:1, their ages ranged from 2 to 9 years, with a mean age 5.6, SD ± 2.11 years. Fifteen patients (75%) were diagnosed before the age of 3 years, while 5 of them (25%) were diagnosed after the age of three years. In the current study, 90% of patients were on speech therapy, 55% were on behavioral therapy, 30% were on risperdal, 15% were on casein, gluten free diet and 75% were on multivitamins. In our study 100% of moderate cases changed to the mild degree, 6% of severe cases changed to mild degree and 31% of severe cases changed to moderate so the lesser the degree of autism the more is the response (Table 1).

There was a statistical significant decrease i.e., improvement in communication, sociability, cognitive awareness, behavior, total score, CARS post HBOT when compared to their level before HBOT  $P < 0.001$ . The more the decrease

**Table 1** Demographic data of the patients.

| Age of patients                                     | No/%               |           |
|---|--------------------|-----------|
| < 5 years   | 6 (30%)            |           |
| 5–9 years   | 14(70%)            |           |
| <i>Age at diagnosis</i>                             |                    |           |
| 1–3 years   | 15 (75%)           |           |
| 3–6 years   | 5 (15%)            |           |
| Sex M/F   | 17/3 (85% vs. 15%) |           |
| <i>Clinical types of ASD (AD/AS/RETT)</i>           | 20/0/0             |           |
| Classification of patients according to CARS scores | Pre HBOT           | post HBOT |
| Mild (21–27)  | 0                  | 5 (25%)   |
| Moderate (28–33)                                    | 4 (30%)            | 5 (25%)   |
| Severe > 34   | 16 (70%)           | 10 (50%)  |
| <i>Treatment</i>                                    | No/%               |           |
| Speech therapy                                      | 18 (90%)           |           |
| Behavioral therapy                                  | 11 (55%)           |           |
| Risperdal   | 6 (30%)            |           |
| Antifungal  | 9 (45%)            |           |
| Casein gluten free diet                             | 3 (15%)            |           |
| Antioxidants, vitamins                              | 15 (75%)           |           |
| Chelation   | 3 (15%)            |           |
| Antiepileptic (Tegretol)                            | 2 (10%)            |           |

ASD: autistic spectrum disorder.

AD: typical autism.

AS: asperger syndrome.

HBOT: hyperbaric oxygen therapy.

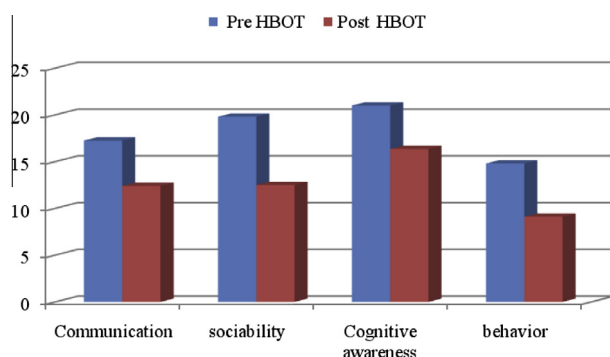
**Table 2** Statistical comparison between ATEC and CARS pre and post HBOT.

| ATEC                | Pre HBOT |       | Post HBOT |       | T     | P      | Improvement (%) | Sig. |
|---------------------|----------|-------|-----------|-------|-------|--------|-----------------|------|
|                     | Mean     | ±SD   | Mean      | ±SD   |       |        |                 |      |
| Communication       | 17.25    | 7.07  | 12.40     | 6.68  | 6.25  | <0.001 | 29.4            | HS   |
| Sociability         | 19.80    | 7.98  | 12.50     | 6.43  | 6.29  | <0.001 | 36.8            | HS   |
| Cognitive awareness | 21.00    | 6.10  | 16.35     | 5.36  | 6.43  | <0.001 | 22.1            | HS   |
| Behavior            | 14.80    | 8.56  | 9.10      | 6.22  | 4.83  | <0.001 | 38.5            | HS   |
| Total score         | 72.40    | 21.57 | 49.10     | 17.98 | 12.52 | <0.001 | 32.1            | HS   |
| CARS                | 37.95    | 5.27  | 32.20     | 6.74  | 7.44  | <0.001 | 15.1            | HS   |

ATEC: autism treatment evaluation checklist.

CARS: childhood autism rating scale/HBOT: hyperbaric oxygen therapy.

HS: highly significant.

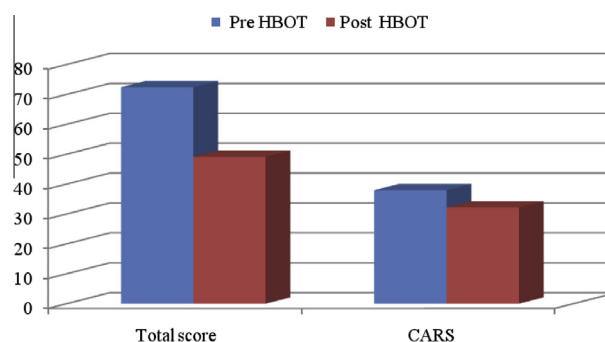


**Figure 1** Histogram showing ATEC subscales pre and post HBOT. It is evident that there is improvement in all ATEC subscales (communication, sociability, cognitive awareness and behavior).

in the score the more the improvement is (Table 2), Figs. 1 and 2. In our study ATEC scores improved by 25.8% in the younger age group compared to 34% in the older age group, CARS improved by 15.4% in the younger age group and 15% in the older age group (Table 3).

Cases with behavioral therapy showed significantly lower mean Cognitive awareness score (meaning increase in mentality) pre and post HBOT, total score (post HBOT) and CARS (post HBOT) when compared to cases without behavioral therapy  $P < 0.05$ . There was no statistical significant difference between cases with and without behavioral therapy as regards the other ATEC parameters pre and post HBOT  $P > 0.05$ .

There was no statistical significant difference between cases with and without casein gluten free diet, respadex, speech therapy, as regards the ATEC subscales, total score and CARS pre and post HBOT  $P > 0.05$ . There was no correlation between age, age at diagnosis, number of sessions and ATEC subscales, total score, CARS post HBOT  $P > 0.05$ . There was a statistical significant increase in the ratio of RCBF (regional cerebral blood flow) to white matter after HBOT in left thalamic region, right prefrontal region, left prefrontal region, right frontal region, left frontal region, right superficial temporal region (Figs. 3–5), as well as left superficial temporal region when compared to their levels before HBOT  $P < 0.05$ . The ratio of RCBF to white matter after HBOT showed increase in right thalamic region when compared to the level before HBOT but the difference did not reach a significant level  $P = 0.07$ . There was no statistically significant difference before and after



**Figure 2** Histogram showing ATEC (total score) and CARS pre and post HBOT. It is evident that there is improvement in both ATEC total score and CARS.

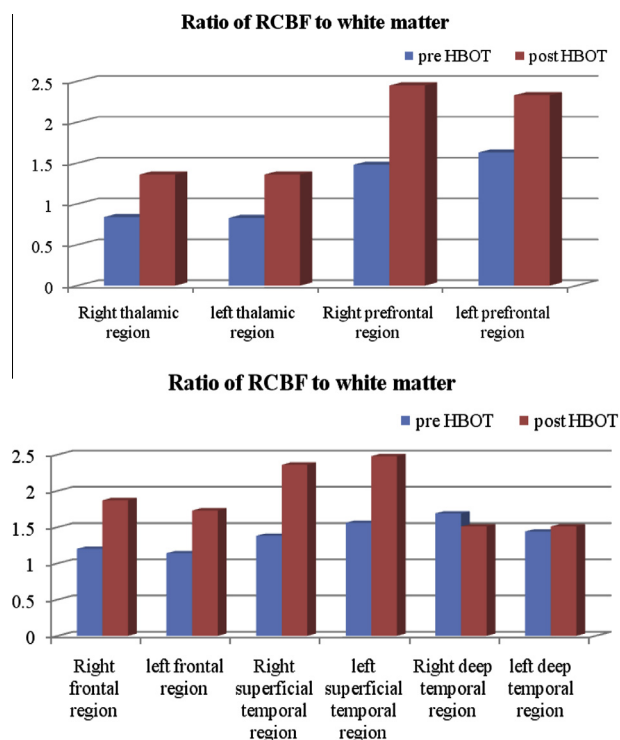
HBOT as regards the ratio of RCBF to white matter in right and left deep temporal regions  $P > 0.05$ .

#### 4. Discussion

Autism Spectrum Disorders (ASDs) are characterized by the presence of impaired development in social interaction and communication and the presence of a restricted activity and interests [14]. The etiology of ASD is not currently known, which may in part explain why numerous widely divergent treatments for ASDs are in regular use. While genetic factors are clearly important, as indicated by high concordance rates among twins and siblings, they alone cannot account for an epidemic that developed in the relatively short period of 10–20 years, however, environmental factors are very likely to account for the major portion of the increased prevalence of autism as many studies showed the presence of higher levels of heavy metals especially mercury in the hair of children with autism as compared to the age and sex matched healthy control [15]. Cerebral hypoperfusion in temporal regions and other brain areas in autistic children has been correlated with repetitive, self-stimulatory and stereotypical behaviors, and impairments in communication. Hyperbaric oxygen therapy (HBOT) might be able to improve each of these problems in autistic children [4]. Specifically, HBOT has been used and can compensate for decreased blood flow by increasing the oxygen content of plasma and body tissues. HBOT has been reported to possess strong anti-inflammatory properties and has been shown to improve immune function [16]. HBOT

**Table 3** Percentage of average score improvement by age.

| Age (years) | ATEC pre HBOT | ATEC POST HBOT | Improvement (%) | CARS PRE HBOT | CARS POST HBOT | Improvement %() |
|-------------|---------------|----------------|-----------------|---------------|----------------|-----------------|
| < 5         | 81.25         | 60.25          | 25.8            | 40.37         | 34.12          | 15.4            |
| ≥5          | 70.18         | 46.31          | 34              | 37.3          | 31.7           | 15              |



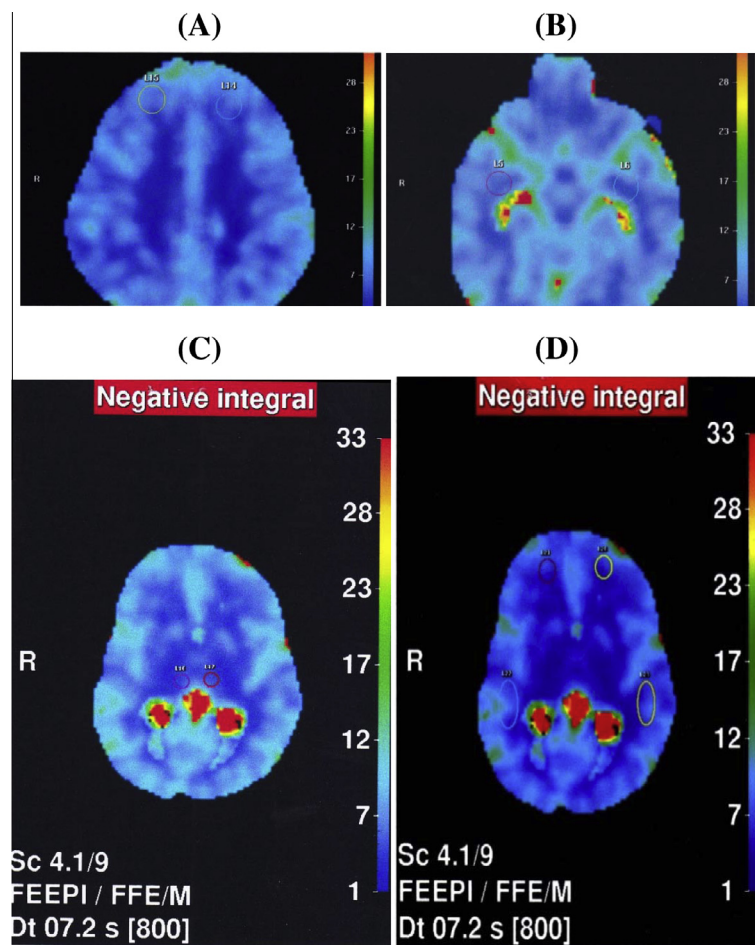
**Figure 3** Histogram showing the ratio of RCBF to white matter pre and post HBOT in different brain areas bilaterally. It is evident that there is increase in regional cerebral blood flow after HBOT in different brain areas.

can overcome the effects of cerebral hypoperfusion by providing more oxygen to the brain and by causing angiogenesis of new blood vessels over time by increasing Vascular Endothelial Growth Factor (VEGF) levels [17,18]. HBOT has been shown to decrease the infiltration of polymorphnuclear leucocytes (PMN's) after an ischemic injury to the brain [19]. In addition, HBOT inhibits neutrophil attachment to blood vessel walls [20] and increases the distance that oxygen can travel in the interstitial space [21]. Treatment with HBOT has been shown to possess potent anti-inflammatory properties in both animal [22,23] and human studies [24,25]. HBOT has been reported to decrease the production of pro-inflammatory cytokines (including TNF-alpha, interferon-gamma, IL-1 and IL-6) in both animal [26,27] and human studies [28] as well as to increase counter-inflammatory IL-10 levels [29]. In one study, HBOT also decreased neopterin levels [30]. The effect of HBOT on reducing inflammation may be mediated through a pressure-related effect and not necessarily by the oxygen delivered. The rationale for using HBOT for the treatment of ASDs is based on the recent findings of oxidative stress [31] and neuroinflammation [32] in ASDs and initial evidence that HBOT may alleviate oxidative stress in rats with pancreatitis [33] and decrease inflammatory responses in rats [34].

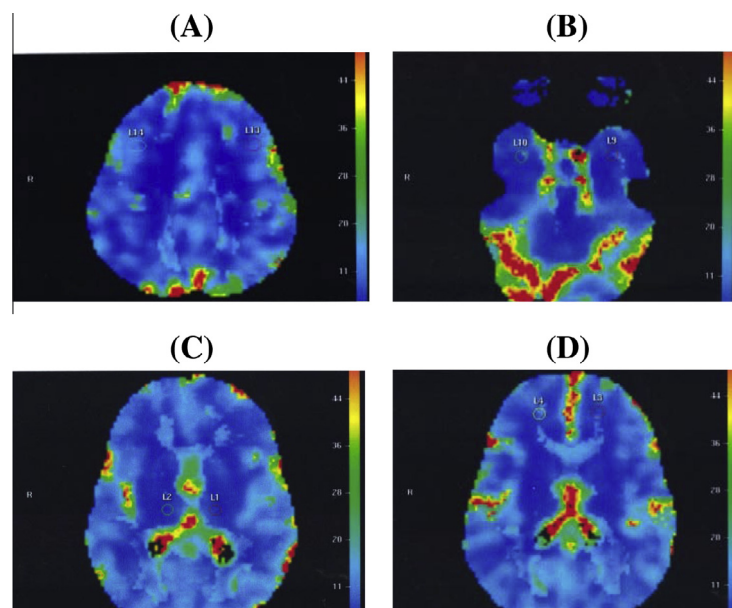
This study was conducted on 20 autistic children, 75% of autistic children were diagnosed before the age of 3 years, while the remaining 25% were diagnosed after the age of three years. Autistic group's age ranged from 2 to 9 years with an average age 5.68 years. These findings are in agreement with Jonson, CP who found that a delay in child's starting to speak around age two brings problems to parents' attention, even though other, less noticeable signs may be present at an earlier age [35]. Other studies reported that parents are often aware of developmental problems in their child from age 18 months, but a diagnosis is often not made until 2 years after the initial expression of parental concern. In some cases diagnosis has not been confirmed until close to age 6 years, which is sometimes associated with delays attributable to access to services and regional variations in diagnosis [36]. In the current study 85% of autistic children were males, and 15% were females, with male/female ratio 5.6:1, and this goes with other studies, one of them involved 2685 patients with autism, the prevalence was more in males than females (ratio of 3.4–6.5) [37], while other investigators reported male:female ratio 2.8–5.5 [38]. Concerning ASD in the present study, 100% of the autistic group were typically autistic (AD). Ninety patients were on speech therapy, 55% were on behavioral therapy, 30% were on risperdal, 15% were on casein and gluten free diet, and 75% were on multivitamins. The key non-biomedical therapy employed by the majority of parents surveyed was speech therapy (75.3%), the next most frequently used therapies were applied behavioral analysis (ABA) and sensory integration which were used by 34.7% and 28.8% respectively. Approximately 50–60% of children were on one of the commonly used diets, e.g., Gluten/Casein Free, Gluten/Casein/Soy free, sugar removed, chocolate removed, and Specific Carbohydrate Diet.

In our study, significant improvement was observed in the ATEC scale in total score, subscales (sociability, sensory/cognitive awareness, and health/physical/behavior, communication) and CARS after completing at least twenty sessions of HBOT at 1.5 ATA and 100% oxygen. The average improvement of ATEC total score in all children was 32.1%, and the average improvement of CARS score in all children was 15.1%. In *another study*, in which six children completed 40, 1 h sessions of low pressure HBOT at 1.3 ATA and 28–30% oxygen, reported an average improvement of ATEC total score in all children as 22.1%, the average improvement of CARS score in all children as 12.1% [6].

As regard to CARS, in our study 100% of moderate cases of autism changed to the mild degree, 6% of severe cases also changed to the mild degree, 31% of severe cases changed to the moderate degree, so the lesser the degree of autism the more is the response. In our study ATEC scores also improved by 25.8% in the younger age group compared to 34% in the older age group, and CARS improved by 15.4% in the younger age group and 15% in the older age group. In contrary to *our study*, other researchers reported that ATEC scores improved by 31.6% in the younger age group compared to 8.8% in the



**Figure 4** MRI brain perfusion in different brain areas (A) prefrontal area, (B) deep temporal area, (C) thalamic area, (D) frontal and superficial temporal area before HBOT.



**Figure 5** MRI brain perfusion in different brain areas (A) prefrontal area, (B) deep temporal area, (C) thalamic area, (D) frontal and superficial temporal area after HBOT showing increased regional cerebral blood flow in all brain areas.

older age group, and CARS improved by 18.0% in the younger age group and 5.6% in the older age group [6]. Our results may be explained by small number of young aged patients (6 patients), however, Golden et al. [39] reported that younger patients tend to have improvements more quickly than older patients. It was proved that older children with autism generally have a higher degree of cerebral hypoperfusion compared to younger children and that hyperbaric oxygen treatment can improve cerebral hypoperfusion [40].

In our study there was no correlation between the number of sessions and both ATEC and CARS post HBOT. On the other hand, other researchers have noted that 50–80 HBOT sessions are typically needed to show significant clinical gains [41]. In our study cases with behavioral therapy showed significant improvement in both ATEC total score (post HBOT) and CARS (post HBOT) when compared to cases without behavioral therapy. In comparison to a recent meta-analysis of studies on early intensive behavioral interventions it was found that the potential effects of HBOT were not additive to the effects of ABA [42].

In our study there was no statistical significant difference between cases with and without multivitamins as regards the ATEC and CARS pre and post HBOT, and this agrees with other study that involved 18 children with autism, who underwent 40 hyperbaric sessions of 45 min duration each at either 1.5 atmospheres (atm) and 100% oxygen, and found that children had similar changes in clinical outcomes whether they were or not taking folic acid and/or methylcobalamin [13].

Regarding MRI perfusion of the brain for the patients, there was a statistically significant increase in the ratio of RCBF to white matter after HBOT in the left thalamic region, right prefrontal region, left prefrontal region, right frontal region, left frontal region, right superficial temporal region, left superficial temporal region when compared to their levels before HBOT. The ratio of RCBF to white matter after HBOT also showed increase in right thalamic region when compared to the level before HBOT but the difference did not reach a significant level. There was no statistically significant difference in the ratio of RCBF to white matter in right and left deep temporal regions before and after HBOT. In agreement with our study, an improvement in cerebral hypoperfusion as measured by SPECT scans in an autistic child after hyperbaric oxygen therapy at 1.3 atm was noted. As HBOT may improve assorted areas of cerebral hypoperfusion, and since these areas may additionally differ in location from child to child, various clinical outcomes could occur [43]. In our study there was a negative correlation between Cognitive awareness score (lower mean cognitive awareness score means increase in mentality) and ratio of RCBF to white matter in left deep temporal region pre HBOT, post HBOT and between behavior score and ratio of RCBF to white matter in right and left thalamic region, left prefrontal region and right deep temporal region post HBOT. Other studies showed that the dysfunction of the superior temporal sulcus may indirectly explain the emotional and cognitive components of autism [44].

Also, Starkestein et al. [2] studied 30 individuals with autism compared to 14 non-autistic individuals. Hypoperfusion of the thalamus as measured by Single Photon Emission Computerized Tomography (SPECT) was observed in the autism group and significantly correlated with repetitive behaviors and unusual sensory interests. Also, a SPECT study of 23 children with autism was compared to 26 non-autistic children,

hypoperfusion of the right medial temporal lobes was found in the autism group and was correlated with obsessive desire for sameness and hypoperfusion of the medial prefrontal cortex and anterior cingulate gyrus was associated with impairments in social interaction and communication [45]. In our study there was no correlation between the patients' ages and ratio of RCBF to white matter either pre and post HBOT [46]. However, other studies showed that hypoperfusion of the prefrontal and left temporal areas worsened and became "quite profound" in autistic children as the age of the autistic child increased. This diminished perfusion correlated with decreased language development. The authors concluded that hypoperfusion "subsequently prevents development of true verbal fluency and development in the temporal and frontal areas associated with speech and communication" [47].

In conclusion, HBOT is a treatment that has recently become quite popular in the ASD community. Its benefits cross a wide range of autistic traits as: it improves language, increases awareness, behavior and socialization. We recommend that the child should undergo a minimum of 40 sessions. Some children may require up to 80 sessions to see benefits. HBOT can be used for any age but a better effect is obtained with early intervention and any degree of autism. However a better effect is obtained with mild and moderate cases. Further research is needed on a large scale in this area being a new modality of treatment in autistic patients.

#### Conflict of interest

The authors declare no conflict of interest. There is no financial and personal relationship with other people or organizations that could inappropriately influence their work.

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