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RESEARCH ARTICLE

ROLE OF HYPERBARIC OXYGEN THERAPY AND RISPERIDONE IN DECREASING SEVERITY OF AUTISM: A CLINICAL TRIAL

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ABSTRACT

Pervasive developmental disorders is umbrella of five disorders: Autistic disorder, Asperger's disorder,Pervasive developmental disorder not otherwise specified, Rett's disorder and Childhood disintegrative disorder. Each one differ than other in degree of symptoms. Generally, all of them called autism. High functioning autistic children are better in response to treatment by either hyperbaric oxygen therapy or combination of hyperbaric oxygen therapy and Risperidone. They have better cognitive abilities. Therefore, this study aimed to determine effects of hyperbaric oxygen therapy and Risperidone in decreasing degree of autism and to predict risk factors that leads to sever autism. The sample consisted of 80 Egyptian autistic children aged 5-7.They diagnosed and followed up by Childhood Autism Rating Scale, version2 (CARS2) between 2015 and 2017. Our studied sample were (80%) male and (20%) female, after adjustment for familial, socio-demographic and individual factors. We concluded that hyperbaric oxygen therapy alone or combination of hyperbaric oxygen therapy and Risperidone has superior effect than Risperidone alone in decreasing degree of autism. In addition, positive consanguinity is a risk factor for severity of autism.

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INTRODUCTION

Pervasive developmental disorder (PDD) is a neurodevelopmental disorder distinguished by dysfunction in sociality, verbal and non-verbal communication, pattern of repetitive behaviors, aggression and irritability (Brentani, 2013). PDD affects about four times more in boyes than girls (Baron-Cohen, 2002). PDD is big medulla of 5 subtypes, these subtypes are autism, Asperger syndrome, Rett's syndrome, PDD-not otherwise specified (PDD-NOS) and Childhood Disintegrative Disorder. They differ in severity. By general, each of them called autism (Muse *et al*., 2012) .The causative factor of PDD is not understood until now. Some studies validated that this disorder related to genetic factor (Johnson *et al*., 2007). Many researchers are trying to understand how genetic factors interact with environmental factors to increase risk of this disorder.

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Many researches are studying environmental factors such as parental age, family medical conditions and other demographic factors (Chaste *et al*., 2012). Many studies tried to determine if vaccines are a possible cause of autism (Taylor, 2014). No drug cure this disorder completely (Witwer, 2007). Risperidone only is FDA approved to treat irritability and aggression of autism (Robb, 2010). Hyperbaric oxygen therapy is a new approach to treat this disorder but not approved until now (Coben *et al*., 2010). The purpose of this study to determine effect of hyperbaric oxygen therapy alone, Risperidone alone and combination of them to decrease severity of autism. Also, to determine relationship between socio-demographic data and severity of autism.

MATERIALS AND METHODS

This is Prospective and comparative controlled randomized Clinical Trial performed on 80 Egyptian autistic Children aged (5-7), diagnosed in Psychiatry Department Assiut University Hospital by The Second Edition of Childhood Autism Rating Scale Standard Version (CARS 2) and followed up For 2 years in Clinical Pharmaceutics Department.

Subjects and Selection Method: The Study Population is 80 Egyptian autistic Children aged (5-7) differ in severity of autism disorder between mild to moderate and sever degree according to The Second Edition of Childhood Autism Rating Scale Standard Version (CARS 2). Then they divided into four groups:

- **The HBOT group:** 20 autistic children received 40, one-hour sessions hyperbaric oxygen therapy. The number of sessions per week allowed is 5 sessions \week, after 6 months from the last session, another 40 one-hour sessions would be taken in the same way.
- **The Risperidone group:** 20 autistic children received Risperidone (dose: 0.25 mg- 0.5 mg \ day) according to weight of child for 8 months. After that, we began the discontinuation phase.
- **The Combined therapy group:** 20 autistic children received hyperbaric oxygen therapy as the first group in addition to Risperidone for 8 months in the same way as second group.
- **The control group:** 20 autistic children received multivitamins as a control group.

Detailed history taking from parents of children after informed consent was obtained for experimentation with human subjects: Age, Sex Of The Patient, prenatal, natal, postnatal history, developmental history cognitive abilities and gross and fine motor function, consanguinity between parents, mothers age, smoking in the family, family history related to similar condition or any psychological or mental disorders. In addition, history of major childhood illness, surgery, medication, and diet. Psychiatric evaluation byCARS2 which include 15 items describe the severity of the disorder. The items are I. Relating to people, Ii. Imitation, Iii. Emotional response, IV. Body use, V. Object use, VI. Adaptation to change, Vii. Visual response, Viii. Listening response, Ix. Taste, smell, and touch response and use, X. Fear or nervousness, Xi. Verbal communication, Xii. Nonverbal communication, Xiii. Activity level, Xiv. Level and consistency of intellectual response, and Xv. General Impressions. Each item is Scored from 1 (No Pathology) to 4 (Severe Pathology) in 0.5 intervals. A total score of 15-29.5 indicated that non-autistic to minimal; a score of 30-36.5 indicated that mild to moderate autism; a score of 37-60 indicated that severe autism (Schopler, 2002). N.B: There was a dropout in the study either from loss of efficacy, cost, no longer interested in medication treatment or lost to follow-up.

Statistical Analysis of Data: Data were expressed as Mean ± SD,(Range) and/or as number (percentage) Of Cases. One Way ANOVA Test was used for quantitative data, Fisher Exact Test for qualitative data and Wilcoxon signed rank test for qualitative data within each group analysis was performed by using The Statistical Package for the Social Sciences (SPSS, Version 20). The Level $P < 0.05$ was considered the cut-off value For Significance.

RESULTS

- Independent sample T test for quantitative data between the two groups.
- Fisher exact test for qualitative data between the two groups
- Significant level at P value < 0.05
- Table 1 shows demographic characteristics of the patients as: age, sex of child, natal history(normal or Cesarean), family history of disorder, residence, consanguinity between parents of child, vaccination, smoking history of parents and mother age(more or less than 30) and relation of these with severity of autism.
- There were insignificant differences between all of these demographic data and severity of autism except consanguinity (p=0.038).

- Simple logistic regression analysis
- OR: Odds ratio
- CI: confidence interval
- Logistic regression is a statistical method for analyzing a dataset in which there are one or more independent variables that determine an outcome (used to predict the probability of occurrence of an event)
- Odds ratio (OR) is one of three main ways to quantify how strongly the presence or absence of property A is associated with the presence or absence of property B in a given population.
- If the OR is >1 the control is better than the intervention.
- If the OR is <1 the intervention is better than the control.
- OR=7.1, it means positive consanguinity is risk factor for severity of autism with confidence interval(1.3-38.2)
- One-way ANOVA test for qualitative data between the four groups.
- Fisher exact test for qualitative data between the four groups
- Significant level at P value < 0.05
- No Significant difference between the four groups at the beginning of the study.
- Wilcoxon signed rank test for qualitative data within each group.
- *: Significant level at P value < 0.05
- Table 4 shows comparison between four groups in degree of severity of autism:
- The first group 20 autistic children treated by hyperbaric oxygen therapy (HBOT), followed up for 2 years and lost 7 children by the end of the study.
- At the beginning, all 20 children are mild to moderate degree of autism and treated by HBOT.
- At the end of 2 years, 12 children became minimal degree of autism while only 1 child remain mild to moderate.
- The second group 20 autistic children treated by Risperidone, followed up for 2 years and lost 7 children by the end of the study.
- At the beginning, 17 children are mild to moderate and3 children are severe degree of autism. They treated by Risperidone.
- At the end of 2 years,2 children became minimal degree of autism while 11 children became mild to moderate.
- The third group 20 autistic children treated by combination of Risperidone and HBOT, followed up for 2 years and lost 5 children by the end of the study.
- At the beginning, 18 children are mild to moderate and 2 children are severe degree of autism. They treated by combination of Risperidone and HBOT.
- At the end of 2 years, 15 children became minimal degree of autism.
- The fourth group 20 autistic children are control treated by multivitamins, followed up for 2 years and lost 3 children by the end of the study.

- At the beginning, 18 children are mild to moderate and 2 children are severe degree of autism. They treated by multivitamins.
- At the end of 2 years, 15 children became mild to moderate degree of autism while 2 became minimal.
- Fisher exact test for qualitative data between the four groups
- Table 5 shows comparison between the four groups at the end of 2years follow up after treatment.
- Significant difference between the HBOT group and both Risperidone and control groups. In addition, there was significant difference between the combined group and both Risperidone and control groups. While, insignificant difference between combined group and HBOT group. At last, there was no significant difference between Risperidone group and control group.

DISCUSSION

Autism is a neurological disorder with difficulty in sociality, verbal and nonverbal communication, pattern of repetitive behaviors, irritability and aggression (Brentani, 2013). Its prev-alence has increased in recent years. There is no clear causes for increasing prevalence (Elsabbagh, 2012). However, may due to changing environmental factors that interact with genetic factors (Landrigan, 2010). Many researchers studied socio-demographic factors lead to exaggerate symptoms of autism. They include certain foods (Reber, 2012), heavy metals, infectious diseases, pesticides, smoking, and vaccines (Sayehmiri, 2015).Therefore, autism is considered one of the pervasive developmental disorders that have two basic elements, developmental delay and developmental deviations (Brambilla, 2003). Our results pointed to that the risk of autism in boys more than girls by 80% of autistic children were males and 20% were females, with male/female ratio 4:1. This finding was agreed with results of Itzchak *et al*. (2010) who found that (81%) of 564 participants were male autistic patients. Shu *et al*. said that autism is more than twice as common in boys as girls (Shu *et al*., 2000). Our results revealed that 93.8% of cases from urban areas with average moderate to high social class while 6.2%from rural areas with relatively lower socioeconomic status. While other study revealed that 48% of cases of autistic patients were of high social class of their parents (El-Baz *et al*., 2011). Most of parents of our patients (87.5%) are non-consanguineous with significance of this finding. Many authors reported similar findings (El-Baz , 2011; Bilder, 2009; Sponheim, 1996).

In our study 15% only had positive family history for similar cases in another study reported positive Family history of autism in 16% of their cases while 1% was negative(18). Muhle et a lreported that families of individuals with autism have increasing of cognitive and behavioral skills for their autistic children (Muhle *et al*., 2004). In our study high mother age (mother >30 years) was found in 33.8 % of autistic children. Reichenberg *et al*. (2004) demonstrated that there was an association between father age and ASD occurrence. They found that generation of 40 years men or older were 5.75 times more likely to have ASD compared with younger men than 30 years, while high mother age showed no association with ASD. Kolevzon *et al*., (2007) found that association between parental age and an increased risk of autism. While Marissa *et al*. (King, 2009) concluded that high mother age, rather than father age, may have greater risk for ASD. In our study, significant decrease in disease severity by using CARS total score. In hyperbaric oxygen therapy (HBOT) group at the beginning of the study the percent of minimal degree autism was (0%), the mild to moderate degree was (100%) and the severe degree was (0%). After 2 years follow up the percent of minimal degree autism was (92.3%), the mild to moderate degree was (7.7%) and the severe degree was (0%).Some studies agreed with us. In a clinical trial studied twenty autistic children were diagnosed by diagnostic and statistical manual of mental disorders, 4th edition criteria, text revised (DSM-IV-TR criteria) and followed up at the Psychiatry Clinic, Children Hospital of Ain Shams University. The patient's ages ranged from 2 to 9 (mean age 5.6, SD ±2.11 years) and consisted of 17 males and 3 females. All patients followed up by Childhood autism-rating scale (CARS) before and after 20 sessions of HBOT.

There was improvement in total score of CARS include (awareness, sociality and communication) post HBOT when compared to their level before HBOT $P < 0.001$ (El-baz, 2014). Ghanizadeh (2012) reviewed 2 randomized controlled trials with a total of 89 participants with autistic disorder (Granpeesheh, 2010; Rossignol, 2009). The first study from the United States (Granpeesheh, 2010) included children 2 to 14 years of age. Sixteen children received HBOT with 1.3 ATA and 24% to 28% oxygen while 18children received control treatment consisting of free airflow for 80sessions of 1 hour each. Following completion of treatment and placebo conditions, all children were rated on the Social Responsiveness Scale. He found no significant difference between groups in social cognition, social communication, or social awareness (all Pvalues of > .05). In addition, no significant differences were found based on total scores on the Autism Diagnostic Observation Schedule Generic tool (Granpeesheh, 2010). In 2002, Heuser *et al*. reported improvement in social interaction and cognitive functioning in a boy with autism after HBOT treatment at 1.3 atm/24% oxy-gen for 10 subsequent days (Heuser, 2002). In another report, 23 patients with autism had various improvements in repetitive behaviors, language and social interaction, with HBOT at 1.5 atm (Harch, 2005).

A prospective study reported the effects of hyperbaric oxygen therapy in eighteen autistic children. Twelve children were treated at 1.3 atm/24% oxygen and 6 were treated at 1.5 atm/100% oxygen for 40 total sessions. This study indicated significant improvements in each group, including motivation, speech, and cognitive awareness ($p < 0.05$ for each (Rossignol, 2007). The Risperidone group in our study at the beginning: the percent of minimal degree autism was (0%), the mild to moderate degree was (85%) and the severe degree was (15%) then after 2 years follow up the percent of minimal degree autism was (15.4%), the mild to moderate degree was (84.6%) and the severe degree was (0%).Some studies agreed with us, an open-label study for 8 weeks examined the effect of risperidone on autistic children 4-17 years old. Risperidone dose was taken as follow: 0.02, 0.04 and0.06 mg/kg/day for first 3 weeks respectively. CARS score decreased significantly, ($P=0.001$) after 8 weeks. Social interactions and communication skills of the patients were improved significantly ($P<0.001$, $P=0.03$, respectively). However, did not show any significant change in stereotypic behaviors (Ghaeli, 2014).

Table 1. Relation between autism severity at the beginning and demographic characteristics of the patients

	Severity at the beginning		P value
	Mild to Moderate	Severe	
	(n=73)	(n=7)	
Age			0.086
Range	(5-7)	(5-7)	
Mean ± SD	5.5±0.8	5±0.6	
Sex			0.139
Male	60(82.2%)	4(57.1%)	
Female	13(17.8%)	3(42.9%)	
Labor			1
Normal	21(28.8%)	2(28.6%)	
Cesarean	52(71.2%)	5(71.4%)	
Family history			1
Absent	62(84.9%)	6(85.7%)	
Present	11(15.1%)	1(14.3%)	
Residence			1
Urban	68(93.2%)	7(100%)	
Rural	5(6.8%)	0(0%)	
Consanguinity			0.038*
Negative	66(90.4%)	4(57.1%)	
Positive	7(9.6%)	3(42.9%)	
Vaccination			-----
Vaccinated	73(100%)	7(100%)	
Not vaccinated	0(0%)	0(0%)	
Smoking			0.700
Not exposed	47(64.4%)	4(57.1%)	
Exposed	26(35.6%)	3(42.9%)	
Mother age			0.758
Range	(24-39)	(26-35)	
Mean ± SD	29.4±3.4	29.9±3.2	
Mother age			1
≤ 30 years	48(65.8%)	5(71.4%)	
>30 years	25(34.2%)	2(28.6%)	

Table 2. Simple logistic regression analysis to detect the predictor of CARS severity

	OR	95% CI	P value
Positive consanguinity	7.1	1.3-38.2	0.023*

Table 3. Comparisons of severity (degrees) at the beginning between the four groups

CARS at begin	HBOT Group (n=20)	Risperidone Group (n=20)	Combined Group (n=20)	Control Group (n=20)	P value
Range	(32-36.5)	(32-38.5)	(32-38.5)	(32.5-38.5)	0.448
Mean ± SD	34.6±1.4	35.3±1.8	35±1.8	35.3±1.7	
Minimal	0(0%)	0(0%)	0(0%)	0(0%)	0.500
Mild to Moderate	20(100%)	17(85%)	18(90%)	18(90%)	
Severe	0(0%)	3(15%)	2(10%)	2(10%)	

Table 4.Comparison between the severity degreesat the beginning and after two years in each group

	Severity at the beginning (n=80)	Severity after 2 years (n=58)	P value
HBOT Group			0.001*
Minimal	0(0%)	12(92.3%)	
Mild to Moderate	20(100%)	1(7.7%)	
Severe	0(0%)	0(0%)	
Risperidone Group			0.025*
Minimal	0(0%)	2(15.4%)	
Mild to Moderate	17(85%)	11(84.6%)	
Severe	3(15%)	0(0%)	
Combined Group			<0.001*
Minimal	0(0%)	15(100%)	
Mild to Moderate	18(90%)	0(0%)	
Severe	2(10%)	0(0%)	
Control Group			0.046*
Minimal	0(0%)	2(11.8%)	
Mild to Moderate	18(90%)	15(88.2%)	
Severe	2(10%)	0(0%)	

Table 5. Comparison of severity degrees after two years between the four groups

CARS (2 years)	HBOT Group (n=13)	Risperidone Group (n=13)	Combined Group (n=15)	Control Group (n=17)	P value
Minimal Mild to Moderate Severe	12(92.3%) 1(7.7%) 0(0%)	2(15.4%) 11(84.6%) 0(0%)	15(100%) 0(0%) 0(0%)	2(11.8%) 15(88.2%) 0(0%)	< 0.001*
P value (multiple comparisons)					
Risperidone Group	<0.001*				
Combined Group	0.464	<0.001*			
Control Group	<0.001*	1	<0.001*		

Another study Mc Dougle *et al*., reported that improvement in social interactions after 8 weeks initiation of risperidone. This improvement was not found to be significant (P=0.07) (McDougle, 200). In an open-label study in 24 autistic patients, treatment with risperidone resulted insignificant improvement in Children's Psychiatry Rating Scale (CPRS) and "sociality" item of CARS after 16 weeks (Masi, 2010). Another double blind randomized clinical trial in 80 patients with autism treated by risperidone for 8 weeks. They found significant improvement in "sociality" subscale of ABC after treatment (Pandina, 2007). The combined therapy group in our study at the beginning: the percent of minimal degree autism was (0%), the mild to moderate degree was (90%) and the severe degree was (10%),then after 2 years follow up the percent of minimal degree autism was (100%), the mild to moderate degree was (0%) and the severe degree was (0%).At last, the control group at the beginning of the study the percent of minimal degree autism was (0%), the mild to moderate degree was (90%) and the severe degree was (10%),then after 2 years follow up the percent of minimal degree autism was (11.8%), the mild to moderate degree was (88.2%) and the severe degree was (0%). All the results at the beginning and after 2 years follow up are significant. On multiple comparison between the results for the four groups, we found that there was significant difference between the HBOT group and both Risperidone and control groups. In addition, there was significant difference between the combined group and both Risperidone and control groups. At last, there was no significant difference between Risperidone group and control group.

Conclusion

Autism is neurological disorders characterized by impairment in several areas of development. This disorder has more degree of severity. We concluded that positive consanguinity is associated with severity of autism and predict it. In addition, hyperbaric oxygen therapy also, combination of hyperbaric oxygen therapy and Risperidone have superior effect than Risperidone alone in decreasing severity of autism.

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List of abbreviations

ABC	Aberrant Behavior Checklist
ASD	Autism Spectrum Disorder
CARS 2	Childhood Autism Rating Scale, version2
CPRS	Children's Psychiatry Rating Scale
DSM-IV-TRcriteria	diagnostic and statistical manual of mental disorders, 4th edition criteria, text revised
HBOT	Hyperbaric Oxygen Therapy
PDD	Pervasive developmental disorder
PDD-NOS	Pervasive developmental disorder not otherwise specified

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