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Comparing the Genetic Detox Ability and Heavy Metal Burden in a Cohort of Samples of Egyptian Children and those with Autistic Spectrum Disorder

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Abstract

The heavy metal burden of patients with Autism spectrum disorders (ASD) has been widely discussed [1-5]. Present knowledge suggests that ASD patients, compared to 'normal's' show a greater metal burden, which may be a cause of the ASD pathogenesis, possibly due to a limited detoxification potential. We thus aimed to evaluate if the metal burden of ASD children is due to comprised detoxification ability, and if missing of enzymes such as the glutathione-S-transferases provide an explanation, or if additional factors play a role. Genetically, we noticed a slight difference in the detoxification ability of the ASD group compared to the Control group. In the ASD group, carrier of the genotype GSTT1 null genotype (i.e. the homozygous loss) are 1.7 times more common as in the Control group and the GSTT1 allele is more frequent in the ASD patient collective. These findings are not statistically significant but indicate a trend. In addition, our data indicates that levels of potentially toxic metals in blood and hair of both groups demonstrate a similar immediate and long-term exposure. However, 36% of the ASD group showed signs of zinc deficiency compared to 11% of the Control group and this points towards inefficiency of the Phase I detoxification pathway. More research is needed to explore the role of other elements in the detoxification pathway.

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Keywords

ASD; Toxic metals; Glutathione S-Transferases; Detoxification pathway; Zinc deficiency

Introduction

Autism is a severe neurodevelopment disorder which involves communication deficits, and stereotypic/repetitive behavior. Associated health problems include neurological defects, developmental delay with communication deficits, verbal and non-verbal, learning disabilities and behavioral abnormalities. Environmental factors such as pollution, including heavy metal overexposure, were implicated in the development of ASD by Volk et al, Roberts and other researchers, and were confirmed in our previous studies on Arab and Indian children [6-8]. It has been outlined many times before that genetic factors influence the etiology of this disorder.

All our previous studies compared the metal burden of ASD patients to that of a healthy population, but never to a healthy population living under similar environmental conditions. In our recent Nigerian study [9], we compared a group of healthy children with ASD children; all living in the same environment in the Niger Delta, a densely populated industrial area of 20,000 km² where environmental regulations are rarely enforced, hence toxic exposure through air, water and soil is high [10-13].

We compared the degree of the metal burden found in both test groups, including their individual detoxification ability involving the glutathione-S-transferase theta 1 (GSTT1) and Glutathion-S-Transferase M1 (GSMT1). These detoxification enzymes are members of a super family of proteins that catalyze the conjugation of reduced glutathione to a variety of electrophilic and hydrophobic compounds and play an important role in the detoxification of potentially toxic metals [14].We used hair analysis, which is a diagnostic tool for the detection of long-term exposure, [15] and tested blood for the detection of trace element deficiencies immediate and toxic metal exposure, [16] with the aim to provide further documentation that would prove environmental exposure as one notable cause of ASD. We used blood to identify if an improperly functioning detoxification pathway plays a role in the etiology of metal intoxication and the development of ASD.

Methods

Purpose: The purpose of this study was to identify if an improperly functioning detoxification pathway plays a role in the etiology of metal intoxication and the development of ASD. All study cases had been previously diagnosed as having ASD applying GARS (Gilliam's Autism Rating Score). All scoring above 100, ranging from moderate to severe ASD. This study admitted a total of 121 participants. Of those, we received 99 hair samples from the ASD group and 22 hair samples from the Control group. We also received 27 blood samples from the Control group and 92 blood samples from the group of ASD patients.

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The mean age of the ASD group was 6.2years; the Control group showed a mean age of 6.4years. All blood and hair samples were collected by the team of Professors Dr. Ehab Ragaa and Dr. Adel Hashish and shipped overnight to Micro Trace Minerals Laboratory (MTM) in Germany. Metal testing was performed under the direction of Dipl.

Ing Albrecht Friedle and Dr. E. Blaurock-Busch via ICP-MS utilizing cell technique. For genetic testing, MTM forwarded samples to Dr. Eckart Schnakenberg of the German laboratory Ipgd (Institut für Pharmakogenetik und genetische Disposition).

Genetic Testing

We tested 26 samples from the Control group and compared these to the ASD group (n = 93) for GSTM1 and GSTT1 deletions, respectively. We selected these glutathione-S-transferases of the detoxification Phase II as literature suggests that reduced Phase II reactions lead to the accumulation of toxins, metals included.

Glutathione S-Transferase M1 (GSTM1)

GSTM1 is produced in the brain, gallbladder,and colon but predominantly in the liver and endocrine tissues. Through enzymatic conjugation with glutathione, GSTM1 functions in the detoxification of environmental toxins and products of oxidative stress, electrophilic compounds, including carcinogens and therapeutic drugs. In individuals with the GSTM1 null genotype this enzyme is missing. As a result, the elimination of certain toxins is compromised. Like all GST enzymes, GSTM1 detoxifies cancer-causing chemicals as found in cigarette smoke such as benzopyrene.(http://www.proteinatlas.org/ENSG00000134184-GSTM1/pathology)

Table 1: Genotype statistics, GSTM1 and GSTT1.

		GSTM1		
	0/0 homozygote missing	**0/1 heterozygote missing**	**1/1 homozygote present**	**Total**
ASD Group	N=50	N=41	N=2	N=93
	53.8%	44%	2.2%	100%
Control Group	N=15	N=10	N=1	N=26
	57.7%	38.5%	3.8%	100%
		GSTT1		

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	0/0	0/1	1/1	Total
ASD Group	N=31	N=38	N=24	N=93
	33.3%	40.9%	25.8%	100%
Control Group	N=6	N=13	N=7	N=26
	23.1%	50.0%	26.9%	100%

Glutathione S-Transferase T1 (GSTT1)

GSTT1 is found in lymphocytes and the liver. It is involved in the detoxification process of a variety of environmental chemicals, such as the ones used in polymer productions and especially organic solvents. Like all GST Enzymes, GSTT1 detoxifies cancer-causing chemicals as found in cigarette smoke. Approximately 15-20% of Caucasians show a complete lack of GSTT1 activity due to inborn deletion of the GSTT1 gene (GSTT1 *0/*0). In individuals with the GSTT1 0/0 genotype this enzyme is missing. As a result, the elimination of certain toxins is reduced [17]. With the deletion of GSTM1 and GSTT1, the detoxification potential is markedly reduced (Table 1).

In the ASD group, it is striking that carrier of the GSTT1 null genotype (i.e. the homozygous loss of GSTT1 gene) are 1.7 times more common as in the control group (OR 1.7; 95% CI 0.6-4.6, p=0.318). Also, the GSTT1 allele is more common in the ASD patient collective. These findings are not statistically significant, but the trend is clear.

Metal testing

We assessed the levels of trace elements and heavy metals in hair and blood of the ASD and Control group, aiming to establish a link between environmental exposure and the genesis of autistic spectrum disorder. In a recent Nigerian study, a comparison of blood and hair values confirmed present and past exposures as the potential cause of the participants' metal burden [9].

Metal analysis of blood and hair

Laboratory diagnostics allow the distinction between present and past metal exposure. If an acute exposure –as diagnosed in blood- remains for weeks or even longer periods, and if the body's ability to eliminate toxins is inadequate, it may be assumed that the increased intake and decreased output contributes to tissue accumulation as reflected in hair [18].

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Sample Preparation and Analysis

Using the Agilent ICP-MS 7500 with Octopole Reaction System (ORS), we tested blood and hair samples for toxic and nutrient elements as outlined in (Table 2). We statistically evaluated mean and standard deviation for each element, and the corresponding statistical significance. Reported are toxic elements with a mean blood concentration exceeding the established 95 percentage reference range. Also noted are potential deficiencies of nutrient elements such as zinc. Elements showing mean values below detection limits are not reported.

Table 2: Isotope listing of elements tested.

Element	Symbol	Isotop		Element	Symbol	Isotop
Lithium	Li	7		Zinn	Sn	118
Beryllium	Be	9		Antimon	Sb	123
Bor	B	10		Jod	J	127
Magnesium	Mg	24		Caesium	Cs	133
Aluminum	Al	27		Barium	Ba	138
Calcium	Ca	44		Lanthan	La	139
Titan	Ti	49		Cer	Ce	140
Vanadium	V	51		Praseodym	Pr	141
Chrom	Cr	52		Neodym	Nd	146
Mangan	Mn	55		Samarium	Sm	147
Eisen	Fe	56		Europium	Eu	153
Kobalt	Co	59		Gadolinium	Gd	157
Nickel	Ni	60		Dysprosium	Dy	163
Kupfer	Cu	63		Erbium	Er	166
Zink	Zn	66		Thulium	Tm	169
Gallium	Ga	69		Ytterbium	Yb	172
Germanium	Ge	74		Lutetium	Lu	175
Arsen	As	75		Hafnium	Hf	178
Selen	Se	78		Tantalum	Ta	181
Rubidium	Rb	85		Wolfram	W	182

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Strontium	Sr	88		Rhenium	Re	185
Zircon	Zr	90		Iridium	Ir	193
Niobium	Nb	93		Platin	Pt	195
Molybdän	Mo	98		Quecksilber	Hg	202
Rhodium	Rh	103		Thallium	Tl	205
Palladium	Pd	105		Blei	Pb	208
Silver	Ag	107		Bismuth	Bi	209
Cadmium	Cd	111		Thorium	Th	232
				Uran	U	238

Blood Metals

Whole blood was collected in EDTA tubes. Of those received, we analyzed 92 blood samples from the ASD group and 27 for the Control group. In the laboratory, 1ml of EDTA blood was acid digested with non-ionic nitric acid, diluted to 5ml with metal-free water. We also tested two plain (empty) EDTA tubes as provided by the Egyptian team for potential contamination. Elevated levels of aluminum and barium were detected as shown in (Table 3).

Table 3: Metal contamination in EDTA blood tubes.

SampleNr	**SampleName**	**Clinical_Information**	**Al-µg/L**	**Ba µg/L**
1X190143	Empty EDTA Tube1	H2O as Simulant Solution	75	67
1X190143	Empty Tube2	HNO3 (3,45%) als Simulant Solution	310	100
DL			10	0.25
Ref.Range			<30	N/A
DL = Detection Limit; N/A = not available				

As a result, these elements were not used for our statistical evaluation of blood samples. It should be noted that in previous studies we also noted this contamination problem in so-called ‘metal-free’ EDTA tubes.

Tube 1X1901043-1 was filled with metal-free water, shaken for 30 minutes before this aqueous solution was processed like a blood sample. The second tube 1X190143-2 was filled

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and shaken for 30 minutes with 2mL metal-free nitric acid (3.45%) before the acidified aqueous solution was processed like a blood sample. Results are in µg/L.

Blood Metal Results

We acknowledge that the limited number of controls in our study does not allow for a good comparison between groups. However, the p-value established between the groups indicates a statistical significance for Magnesium, Molybdenum, Lead, Antimony, Titanium and Vanadium. Highlighted are mean values for elements bordering or exceeding existing reference ranges. It must be noted that the borderline mean value of 1.83µg/L Molybdenum as compared to the reference range of 1.8µg/l is considered analytically insignificant; hence both groups should be looked upon as nutritionally adequate. Similarly, the mean concentrations for the nutrient element magnesium may be considered nutritionally adequate. For Zinc, 36% of the ASD group showed blood levels <4mcg/L reflecting zinc deficiency, compared to 11% of the Control Group. This along with the significant p-value may be the most significant finding of this study.

Significant p-values were noted for Antimony and Lead in both groups, however, the mean blood lead levels for the Control Group were higher for both elements, indicating a higher immediate exposure of the Control Group.

Table 4: Comparison of blood metals between ASD and Control Group, Summary, Anova Single Factor

Groups	Count	Sum	Average	Variance	p-value between groups	Reference range in µg/L
As - Control	22	117.35	4.35	20.38		
As - ASD	92	306.50	3.33	14.64	0.248	<10
Cu- Control	27	25.62	0.95	0,038		
Cu- ASD	92	84.96	0.92	0.021	0.461	0.6 to 1.36
Ge - control	27	28.59	1.06	0.079		
Ge - ASD	92	107.57	1.17	0.104	0.112	<5.4
I - control	27	1092.76	40.47	149.60		
I - ASD	92	4578.63	49.77	2757.73	0.365	15 to 132
Mg - control	27	1046.55	38.76	32.10		
Mg - ASD	92	3855.52	41.91	36.11	0.017	25 to 45.8
Mn - control	27	386.13	14.30	17.28		
Mn - ASD	92	1512.73	16.44	48.10	0.130	7.1 to 20.00

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Mo - control	27	49.44	1.83	1.11		
Mo - ASD	92	133.29	1.45	0.42	0.023	0.5 to 1.8
Ni - control	27	83.06	3.09	3.35		
Ni - ASD	92	377.61	4.10	16.10	0.208	<2.00
Pb - control	27	1049.85	38.88	509.67		
Pb - ASD	92	2817.12	30.62	212.37	0.025	<35.00
Sb - control	27	58.92	2.18	45.67		
Sb - ASD	92	55.26	0.61	0.34	0.027	<3.5
Se - control	27	3854.28	142.75	765.94		
Se - ASD	92	10812.79	117.53	593.25	1.146	40 to 100
Sr - control	27	1598.22	59.19	391.37		<50 adults
Sr - ASD	92	4846.05	52.67	318.70	0.106	<20 children
Ti - control	27	127.05	4.71	5.05		
Ti - ASD	92	556.01	6.04	8.65	0.031	<7.7
V - control	27	17.46	0.65	0.41		
V - ASD	92	40.75	0.44	0.14	0.041	<0.8
Zn - control	27	212.75	7.88	45.39		
Zn - ASD	92	410.87	4.66	1.10	6.72E-06	4 to 7.5
Significant = p- value <0.05						

Hair Metal Testing

Micro Trace Minerals has performed hair mineral analysis since 1984 and developed reference ranges on various populations, following standard laboratory procedures.

Hair samples received for this study had been cut 3-5cm from the scalp and no chemically treated hair was accepted for testing. Samples were washed with non-ionic detergents and rinsed with non-ionic water before drying in a special, designated oven. The washed and dried hair was weighed close to 100mg, before it was acid digested with non-ionic nitric acid and diluted to 5ml with non-ionic water. Strict quality control measurements and licensing requirements were followed, including the use of certified quality control standards. Table 5 indicates that the p-value established between the groups reflect a statistical significance for

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Copper, Lead, Strontium and Vanadium. Highlighted are mean concentrations exceeding reference ranges.

Table 5: Evaluation of hair metals for both groups, Summary: Anova Single Factor

Groups	Count	Sum	Average	Variance	p-value between groups	Reference range in µg/g
Al - Control	22	630	28.61	302.13		
Al - ASD	99	2409	24.33	202.23	0.222	<8
As - Control	22	1.27	0.06	0.002		
As - ASD	99	7.02	0.07	0.007	0.467	<0.2
Cu - Control	22	685.78	31.17	824.69		
Cu - ASD	99	1871.77	18.91	96.97	0.0007	6.7 to 37
Ge - Control	22	0.12	0.005	1.34		
Ge - ASD	99	0.57	0.005	0.0001	0.859	<0.5
I - Control	22	65.65	2.98	42.08		
I - ASD	99	217.42	2.20	46.03	0.620	1.5 to 3.5
Mg - control	22	3259	148.15	10270		
Mg - ASD	99	10669	107.77	24589	0.251	20 to 115
Mn - control	22	132.06	6.00	122.60		
Mn - ASD	99	418.10	4.22	86.95	0.436	0.07 to 0.5
Mo - control	22	1.78	0.08	0.003		
Mo - ASD	99	6.47	0.07	0.001	0.076	0.02 to 1.0
Ni - control	22	19.42	0.88	0.59		
Ni - ASD	99	59.76	0.60	0.49	0.099	<0.85
Pb - control	22	187.55	8.53	83.85		
Pb - ASD	99	478.51	4.83	25.89	0.010	<3
Sb - control	22	3.03	0.14	0.01		
Sb - ASD	99	11.27	0.11	0.02	0.461	<0.2
Se - control	22	13.66	0.62	0.02		

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Se - ASD	99	117.51	1.19	28.83	0.610	0.4 to 1.5
Sr - control	22	196.67	8.94	34.71		
Sr - ASD	99	521.05	5.26	61.25	0.040	0.11 to 4.28
Ti - control	22	32.29	1.47	1.15		
Ti - ASD	99	147.55	1.49	2.36	0.947	<0.65
V - control	22	17.91	0.81	0.59		
V - ASD	99	46.40	0.47	0.40	0.028	0.01 to 0.15
Zn - Control	22	4489	204	27099		
Zn - ASD	99	18716	189	14681	0.625	110 to 227

Elements with a mean concentration below the detection limit (DL) are not included.

Significant = p-value <0.05

When comparing the p-values between the groups, only lead (Pb) showed a statistical significance for blood (0.025) and hair (0.010), however, the mean lead (Pb) concentration of blood and hair is higher in the Control Group (Table 6).

Table 6: Comparison of Mean Lead Concentration in blood and hair of both groups.

	Control hair mcg/g	**ASD- hair, mcg/g**	**Ref.Range hair**	**Control Blood µg/L**	**ASD blood µg/l**	**Ref.Range blood**
Lead (Pb)	8.5	4.83	<3	38.88	30.62	35

Comparing Nutrient Metal Results

An agreement in statistical significance was found for Vanadium only, but when we compared the mean blood concentrations for both groups, both groups showed blood levels within the accepted range: 0.44µg/l for the ASD Group and 0,65µg/l for the Control Group compared to a reference range of <0.8µg/l. For hair, we noted mean V concentrations for the Control Group (0.81µg/g V) and the ASD Group (0.47µg/g V) compared to a reference range of 0.10 to 0.15µg/g. We have no explanation for this. Skalny noted that Micronutrients, including selenium (Se), are frequently used for ASD management. However, their efficiency remains unclear [19].

We noted a lower mean blood selenium concentration of 117mcg/l for the ASD group compared to the Control group's mean of 143mcg/l. Similarly, hair mean concentrations were higher in the ASD group, but compared to existing reference ranges both groups showed values within range. Neither group shows acute or long-term deficiencies. Since selenium is

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an important antioxidant. It may be considered a protective mechanism against toxic exposure. The p-value between groups for Zn in blood showed significance. For the ASD group, 36% showed low blood zinc levels compared to 11% of the Control group, reflecting a classic zinc deficiency. However, mean hair levels did not reflect a long-term, chronic problem. Of the Control group, 18.6% showed test values below the reference range of 110 µg/g, compared to 19% of the ASD group. Zinc deficiency has been associated with ASD [20,21].

Conclusion

Genetic evaluation of the glutathione-S-transferases GSTM1 and GSTT1 suggests that the genotype GSTT1 null genotype (i.e. the homozygous loss) may be more common in ASD patients. While we did not locate a greater metal burden in our ASD group, we could demonstrate that zinc deficiency as seen through blood testing is 3x more prevalent in the ASD group. Zinc deficiency reduces the function and activity of the SOD1 enzyme and inactivity of the SOD enzyme disturbs the cell metabolism. Since zinc is needed for proper functioning of the zinc-containing Phase I Enzyme SOD1 (CuZnSOD), playing a role in the Metallothionine gene expression of the detoxification system, we can safely assume that further genetic testing in addition to blood metal testing is needed to evaluate the combined effect of toxic metal burden in the presence of zinc deficiency.

We thus recommend a larger and more detailed genetic study comparing SOD1 enzyme function with blood zinc levels. It also seems necessary to compare male and female data as zinc deficiency may be more common in males than females.

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