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Oxidative stress in children with Down syndrome.

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Abstract

Elevated oxidative stress in Down syndrome due to elevated levels of superoxide dismutase 1 can be assessed by estimating the products of lipid peroxidation - malondialdehyde and protein carbonylation .The present study included 31 clinically diagnosed and karyotypically confirmed Down syndrome children with equal number of age and sex matched controls. The levels of malondialdehyde (6.1 ± 2.5 µmol/L vs 3.1 ± 1.2 µmol/L) and protein carbonylation (5.0 ± 2 nmol/mg of protein vs 3.4 ± 0.4 nmol/mg of protein)were significantly elevated when compared with controls with p value of <0.001 and <0.0001 respectively. There was a significant increase in oxidative stress in children with Down syndrome as evidenced by elevated levels of malondialdehyde and protein carbonylation. Antioxidants may have beneficial effect in cases of Down syndrome.

Keywords: Down syndrome , Oxidative stress, Chromosomal analysis, Superoxide dismutase 1 (SOD -1), Malondialdehyde (MDA), Protein carbonylation (PCO)

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Introduction

An imbalance between oxidants and antioxidants in favour of the oxidants, potentially leading to damage, is termed 'oxidative stress'[1]. Antioxidant defence involves both enzymatic and non enzymatic pathway which protect against oxygen radical damage [2]. Superoxide dismutase 1(SOD-1)is an antioxidant enzyme encoded on 21 chromosome (21q22.1) which causes dismutation of superoxide anion into hydrogen peroxide and oxygen. The activity of SOD-1 is elevated in Down syndrome [3,4] due to gene dosage effect. This elevated activity of SOD-1 induces oxidative stress in Down syndrome by elevating reactive oxygen species.

Malondialdehyde (MDA) reflecting the free radical burden was elevated in some studies [5-7] suggesting oxidative damage in Down syndrome without any age and gender variation [7]. Normal levels of MDA was also observed [3] .The MDA estimation alone is commonly done for estimation of products of oxidative damage. There is no published data regarding protein carbonylation (PCO) estimation as products of oxidative damage in Down syndrome. In the present study Oxidative stress in Down syndrome has been evaluated through the estimation of products of oxidative damage like plasma MDA and plasma PCO .

Material and Methods

The study group consisted of 31 clinically diagnosed Down syndrome children between 3 months and 14 years (mean ± SD, 3.64 ± 3.39 yrs) of age with 18 males and 13 females. The control group consisted of same number of age and gender matched normal children. Children with infections and other severe illness were excluded. Based on age both cases and controls were divided into three groups, Group I: 3 months to 4 yrs(n=19), Group II: 4 to 8 yrs(n=06) and Group III : 8 to 14 years (n=06). The study was approved by Institute Ethics Committee and informed written consent was obtained from the parents of the study and control group . Blood samples were collected by venipucture. The clinical diagnosis of Down syndrome was confirmed by conventional lymphocyte cell culture [8] and the chosen metaphase spreads were screened using automated karyotype software, Ikaros Metasystem of Carl Zeiss, Germany. Separated plasma was used for the estimation of plasma MDA and PCO. MDA and PCO were assayed by Satoh [9] and modified Levine [10] method and the absorbance were measured at 540 and 366 nm respectively using UV-VTS Spectrophtometer 117, Systronics.

The parametric Unpaired t test and non-parametric Mann Whitney test were used to estimate differences between

case and control group at a significance threshold of $p < 0.05$. All statistical test were performed with the Graph-Pad InStat 3 software.

Results

Chromosomal analysis showed pure trisomy 21 in all 31 cases in the study group. Other variants of Down syndrome like translocations, mosaicism and partial trisomy were not observed in the present series.

Bochemical analysis showed significantly elevated levels of MDA and PCO in cases when compared with controls[Tables1,2] and [Figures 1,2] . At the level of individual age groups ,the increase in MDA in cases when compared with controls were significant in all age groups except in eight to fourteen years(GroupIII) [Table 1, Figure 3] . Increase in PCO were significant in all age groups and their levels decreased with the advancement of age in both case and control groups [Table 2 and Figure 4].

Table 1. *MDA levels in cases with Down syndrome and controls*

Age Group	Cases (µmol/L)	Controls (µmol/L)	*p* value
Group I	6.0 ±2.8	2.8 ± 1.3	**0.0002**
Group II	6.7 ±2.5	3.3 ± 0.8	**0.0102**
Group III	5.8 ± 1.4	4.0 ± 0.5	0.1320
Whole group	6.1 ± 2.5	3.1 ± 1.2	**< 0.001**

Table 2: *PCO in cases with Down syndrome and controls*

Age Group	Cases (nmol/mg of protein)	Controls (nmol/mg of protein)	*p* value
Group I	5.2 ± 2.4	3.5 ± 0.4	**< 0.0001**
Group II	5.2 ± 1.2	3.4 ±0.4	**0.0065**
Group III	4.2 ± 0.5	3.0 ± 0.1	**0.0022**
Whole group	5.0 ± 2	3.4 ± 0.4	**< 0.0001**

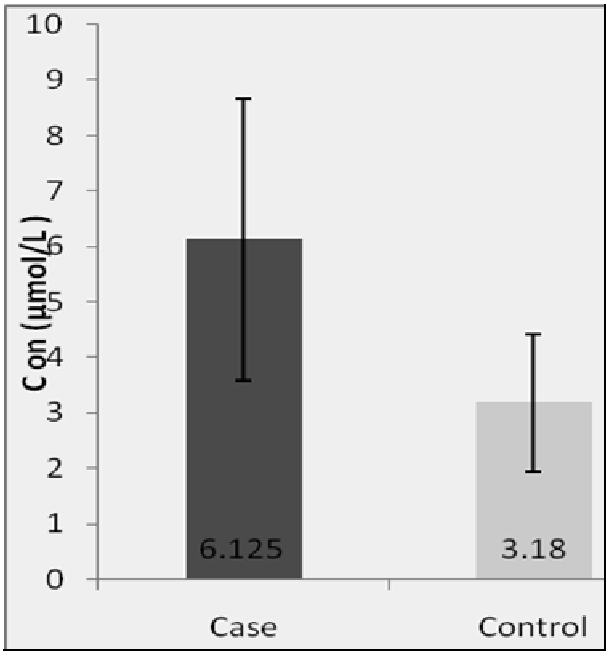

Figure 1*. MDA levels in cases and controls*

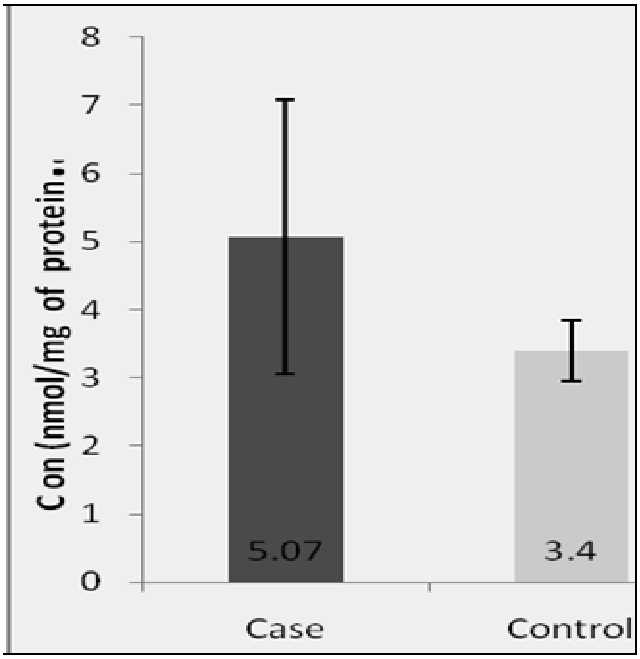

Figure 2. *PCO levels in cases and controls*

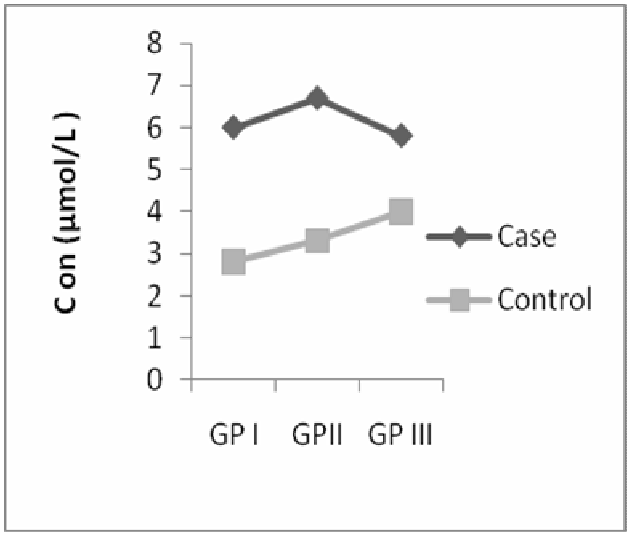

Figure 3. *Variation of MDA levels in different age groups among cases and controls*

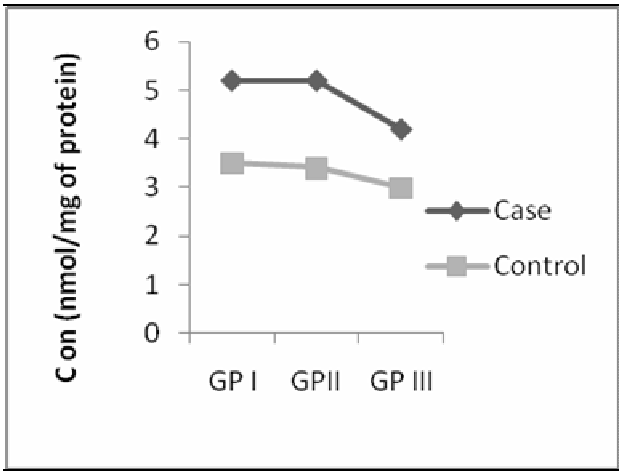

Figure 3. *Variation of PCO levels in different age groups among cases and controls*

Discussion

The oxidative stress results indicate damage to critical cellular macromolecules including DNA, lipids, and proteins[2,12] .It was thought to be mediated via iron catalyzed Haber –Weiss reaction .The hydroxyl radical which is formed initiates a chain reaction which leads to lipid breakdown through peroxidation and breakdown of cell membrane [2,11].

Oxidative damage to unsaturated fatty acids in cell membrane and plasma lipoproteins leads to the formation of lipid peroxyl radicals, then highly reactive MDA (dialdehydes) which is elevated in children with Down syndrome in the present series similar to previous studies [5- 7]. These lipid radicals can diffuse through membranes, thus modifying the structure and function of the membrane resulting in a loss of cell homeostasis. Further it can chemically modify proteins and nucleic acids [2,12] .Thus the total body free radical burden can be estimated by measuring the product of lipid peroxidation , MDA [2].

Proteins are also easily attacked by ROS directly or indirectly through lipid peroxidation[2,12]. Proteins can become modified by a large number of reactions involving reactive oxygen species. Among these reactions, carbonylation has attracted a great deal of attention due to its irreversible nature[13].This protein carbonylation (PCO) is also elevated in children with Down syndrome in the present series. Protein oxidative damage can result in the modifications in structure, enzyme activity, and signaling pathways[12].Thus PCO has been used as a marker of oxidative damage to the tissue.

The elevated levels of products of oxidative damage reflects significant oxidative stress in Down syndrome. There may be a role for using antioxidants to alleviate the symptoms and morbidity in children with Down syndrome.

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