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RESEARCH ARTICLE

EFFECT OF ARSENIC IN THE ETIOLOGY OF DOWN SYNDROME CASES IN POPULATION OF WEST BENGAL

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A B S T R A C T

Down Syndrome (DS) is a serious autosomal chromosome aberration compatible with post-natal survival. It is the most common live-born birth defect in humans. Recent findings suggested that different environmental factors are responsible for DS birth. A possible relationship has been found between the etiology of DS and potential role of heavy metal, especially arsenic, but this complicated association is mostly unknown. The aim of our present study was to examine levels of arsenic in hair of DS child and also to establish a possible relationship between DS and arsenic. A case control study was conducted with sixty DS cases and their Parents in and around Kolkata, India. DS children participated in the study were confirmed after performing karyotyping. The level of arsenic in hair samples were estimated by atomic absorption spectrophotometer. It had been found that the parents of DS child had body burden level and toxic level of arsenic. Most of the DS child had high concentration of arsenic in the hair. Thus it can be concluded from our study that parents possessing high arsenic concentration (both body burden and toxic level) may give birth to DS baby and hence high levels of arsenic in the body of parents may be an etiological factor for DS cases.

INTRODUCTION

Down Syndrome (DS) is the most serious autosomal chromosome aberration compatible with post-natal survival and common live-born birth defect in humans. DS is a relatively common congenital malformation having physical abnormalities of the face, eyelids, tongue and other parts of the body with retarded physical and mental growth (1968). The defects vary in severity, from mild to serious developmental disabilities. The affected individual has either a somatic cell of 46 chromosomes involving translocation of D 15/G 21 chromosomes or 47 chromosomes with trisomy 21. This disorder is named after John Langdon Down, the British doctor who first described this syndrome. (Down, 1866). This disorder is associated with major and minor difficulties in structure. Often Down syndrome is associated with some impairment of cognitive ability.

In all ethnic groups, the incidence of DS occurs in 1 out of 800 to 1000 live births. The increase in the incidence of DS cannot fully be explained by genetic defects and it is thought that environmental events may play a role as an additive either through interaction with some genes or directly. Although these statistics are heavily influenced by the age of the mother, other factors may also play a role. The possibility of an etiological role for environmental factors such as toxic heavy metal exposure has risen after a sharp increase in DS.

Heavy metals are elements that exhibit metallic properties, which may be toxic and, can be considered as worldwide environmental health hazards (Akyuzlu *et al*., 2014). Humans can come under exposure to heavy metals through water, building materials, fertilizers, silver dental fillings, industrial paint, chemical products, fish that is high in mercury, mercury-containing preservatives in vaccines, and many more. Among heavy metals, lead, arsenic, mercury and cadmium can cause abnormal fetal developmental behavioral abnormalities, birth and neurological defects, immune dysfunctions. Although these abnormalities are similar to symptoms of the DS, it is not known how these metals affect the development of DS. During pregnancy, the fetus in herit heavy metals (Fido *et al*., 2005) and a growing fetus is more prone to toxicants due to both the incomplete blood - brain barrier and the decreased capacity for drug detoxification (Rodier *et al*., 2000). Furthermore, the lack or excess of essential minerals (trace elements) may increase the toxicity of metals (Fido *et al*., 2005). Among all these heavy metals, arsenic is our interest of study.

Arsenic is a well known toxin. Based on epidemiological evidences, arsenic is considered a human carcinogen. Arsenic is mainly present in two valence states: As^{3+} (arsenite) and

As^{5+} (arsenate). Arsenite is considered to be more potent and genotoxic than arsenate. Arsenic is released in the environment by natural means such as solubilization from geologic formations into water supplies. Many evidences have been found stating that arsenic acts indirectly with other agents to ultimately enhance to specific genotoxic effects that may lead to carcinogenesis. Arsenic is a well known agent that can affect chromosomal damage, induced by a DNA cross linking agent 1, 3-butadiene diepoxide (Yager *et al*, 1993). But most investigators have been unable to induce direct gene mutation. Inhibition of DNA repair mediates the specific co-clastogenic effect of arsenic. The repair inhibition may be a basic mechanism for the comutagenicity and presumably the cocarcinogenicity of arsenic. Arsenic exposure is responsible for specific enhancement of effects related to genotoxicity that may be important to development of cancer. Thus, the current study investigates the relationship between DS and level of arsenic.

MATERIALS AND METHODS

Study Subject

Sixty DS cases were screened among 323 abnormal cases in the cytogenetics unit of the Genetics Department of Ramakrishna Mission Seva Pratishthan. Sixty cases were confirmed DS after performing karyotyping of 323 cases. All procedures were done with the informed consent of participants' parents. Genetic Counseling was done with the help of counselors and psychiatrist of Ramakrishna Mission Seva Pratishthan Hospital.

Cytogenetic Analysis of the Patients

Blood cultures were done for analyzing chromosome aberrations as per routine procedures (Moorhead *et al*., 1960, Sharma and Talukder, 1974). Karyotyping was done on index patients. The banding technique was applied whenever necessary.

Leucocytes rich plasma (0.5ml) was added to 5 ml culture media supplemented with PHA M (0.04ml/ml of culture media) and 20% fetal bovine serum and incubated at 37º C for 72 hrs. Colchicine was added at 70 h of culture. After 2 hrs, culture was centrifuged at 1000rpm for 10 min, treated with pre-warmed KCl (0.075M) for 15 min. Then it is fixed in methanol: acetic acid (3:1) for 10 mins. Fixatives were removed by centrifugation and two more changes of fixative were performed. Fixed cell suspension was laid on clean grease-free glass slide and air-dried and stained with aqueous Giemsa. 100 metaphase plates were scored randomly for analyzing chromosomal aberrations.

Hair sampling

A tuft of hair of the DS child was cut off from the scalp in the occipital region with a surgical stainless steel scissor and stored in polyethylene bags at room temperature. Hair samples were also obtained from their parents. Before analysis, samples were digested with 5ml of concentrated nitric acid and 3ml of concentrated sulfuric acid.

Metal analysis

Flow injection-hybrid generation atomic absorption spectrometry (FI-HG-AAS) at 327nm was used for estimation of arsenic in the collected biosamples. A Perkin-Elmer model 3100 AAS with a Hewlett-Packard-Vectra 386/25N computer with GEM software, Perkin-Elmer EDL System-2 and arsenic lamp (lamp current 400mA) were used for this purpose.

RESULTS AND DISCUSSION

Level of Arsenic Estimated

The present study states that body burden level of arsenic (250-1000 µg/Kg) was present in the parents of DS baby, as shown in Table 1. It states that all DS child had high concentration of arsenic. Concomitant exposure to arsenic may have severe effects on neurodevelopment of children. The present study aimed to meaure the levels of arsenic in DS child and their parents using atomic absorption spectrophotometry and to find out whether arsenic has any role in pathogenesis of Down syndrome.

It has been found that the parents of DS child have body burden level (250-1000 µg/Kg) and toxic level of arsenic (>1000 µg/Kg). Arsenic can easily cross placenta during pregnancy. This toxic heavy metal is a sulfhydryl-reactive metal and even at low exposure it has harmful effects. Most of the DS child had high concentration of arsenic in the hair as arsenic is mostly deposited in keratin rich tissues, such as hair.

Environmental pollutants have some potential to cause Down syndrome through postconceptional teratogenic action (maternal) or preconceptional mutagenic action (maternal or paternal). It was stated in the village of Hungary in 1990s (Czeizel *et al*., 1993) increment of teratogenic births, including that of DS. Water contamination with pesticide trichlorfon has been reported to cause an outbreak of DS birth incidence. In Woburn, Massachusetts, toxic chemicals (industrial solvents, mainly trichloroethylene) from a waste disposal site were detected in municipal drinking water wells (Dolk & Vrijheid, 2003) and people of this area were reported with increased incidence of several congenital anomalies. Lagakos *et al*., (1986) followed up this finding by compiling an exposure score for residential zones in Woburn, using information on what fraction of the water supply in each zone had come from the contaminated wells annually since the start of the wells. The authors found a positive correlation between contaminated water use and higher birthrate of DS in that locality.

Table 1 Level of Arsenic estimated

No. of Families	Type	Level of Arsenic(µg/kg)[mean±SD]
60	Child	1317.17±1135.64
	Parents	739.45±469.88

SD: standard deviation
n.b.: normal level of arsenic: 80-250 µg/Kg., toxic level of arsenic: >1000 µg/Kg., body burden level of arsenic: 250-1000 µg/Kg.

CONCLUSION

DS bables are always at an increased risk for certain health problems. Congenital heart defects, increased susceptibility to

infection, respiratory and hearing problems, obstructed digestive tracts, sleep apnea and childhood leukemia occur with greater frequency in DS child. So for the proper treatment of the above mentioned diseases early diagnosis is necessary. DS baby becomes a mental and economic burden to the families. Thus, resources such as the Down Syndrome Health Care Guidelines and specialized growth charts can further assist families and medical professionals in providing appropriate medical and preventive care.

It can be concluded from this study that parents possessing high arsenic concentration (both body burden and toxic level) may give birth to DS baby. Thus one must reduce exposure to potential teratogens (especially arsenic) before pregnancy in order to prevent DS child and awareness of the uncertainties regarding environmental pollution when addressing paternal concerns are needed by the prenatal service providers.

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