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High Rates of Birth Defects in Fallujah, Iraq: Radiological and Chemical Pollution of the Affected Children and their Parents

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Authors' contributions

This work was carried out in collaboration among all authors. Authors STAA and MT designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author AAM managed the analyses of the study. Author AMAE managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Lack of birth registers hindered knowledge of the frequency of birth defects (BD) in Fallujah, Iraq and comparison of changes in prevalence in time. One study found correlation between BD presentation and teratogenic metal load [1].
Methods: We obtained reproductive history, kin health, environmental exposure and historical residence of families. Hair was sampled from the nape of the neck from families and analyzed by ICP/MS for metal content.
Findings: BD in newborn in 2010 were about 14.7% [2]. Data of reproductive history from 56 couples with child, overcoming the lack of previous data, shows pattern of increase in BD presentation since 1991. Information on parent's immediate kin in more than 1000 people, supports that BD are sporadic events. High residential stability of families allows to rule out local clusters for BD. Focus on load for ten teratogenic and carcinogenic metals (V, Cr, Co, As, Mo, Cd, W, U, Hg,

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Pb) in hair of 43 BD children and 103 their parents, and of 11 healthy newborns and 16 their parents, compared with that of 10 children and 8 adults controls outside the war area, shows that metal contamination is diffuse in the whole Fallujah population and is present already in newborn children hair. Absolute levels of major teratogenic and carcinogenic contaminants (V, Co, Mo, U and Pb) were significantly higher in Fallujah people than in controls from other areas, with Pb levels in BD children higher than other newborns in Fallujah.
Interpretation: Unusual high prevalence progressive in time and increased load of teratogenic metals even in new born hair are reported in Fallujah population. The extensive metal contamination persistent in people's hair in post-war environment and the composite metal load might be a major factor in the increase in time of stochastic events that lead to BD presentation.

Keywords: Fallujah; congenital anomalies.

1. INTRODUCTION

Understanding potential long term effects of recent wars on civilian's health requires monitoring rates of birth defects, cancers and chronic pathologies. Often, lack of pre-existing records constitutes hindrance. In Fallujah, alarm on severely declining reproductive and children health come from doctors, reports from human right groups and political figures [3].

Moreover, modalities of the presentation of BD, relative frequencies, and causes of their recent increase have not been investigated, nor teratogens have been searched for, and mechanistic aspects remain largely unknown till 2011 when the 1st study on limited number of babies with birth defects & their parents done & showed strong correlation between the development of birth defects & the presence of metal load in the investigated sample.

A first task is to collect recent data on prevalence of BD and to attempt a reconstruction of past events; recording reproductive history at registration, with specific questionnaire, is a valuable mean to achieve that aim [4]. Together with the information on health status (BD presentation) within members of the immediate family of the parents of BD children, this information allows to dismiss that monogenetic, high penetrance genetic factors pre-exist in the parents of BD children [5].

Candidate gene effectors are unknown for most structural BDs, and for all a relevant component, generically called, of environmental and/or maternal effect is acknowledged [6]. It is unknown the number of genes contributing to anencephaly in humans, and, in mice.

Anencephaly is attributed to multifactorial combinations of hypomorphs and low-penetrance heterozygotes [7]. CHD have various phenotypes, sometimes compounded with different cardiac-unrelated features and cohort studies detected with very low frequency single genetic mutations putatively involved, while approximately 30% of CHD and tetralogy of Fallot (TOF) are associated with wide genomic rearrangements (chromosome translocation, copy number variation and chromosome trisomies) [8]. Combinations of genetic and non-genetic factors is associated to inheritance of CLP in mice [9]. Also in mice, synpolydactyly is linked to Hoxd13 mutations and its manifestation is dependent upon environmental factors [10].

The traditional paradigm of prevalence data surveillance has been that detection of a particularly high prevalence of BD in one particular population, or a sudden increase in prevalence over time, can help identify possible environmental causes. Presence of teratogenic metals in the war/post-war environment is expected because of the weapon systems used and proofs of fact of their presence in weaponry used in the Middle East wars were reported [11]. Metals persist in environment, are up taken via respiratory, skin contact and ingestion of contaminated water or food, and accumulate and persist in the hair of exposed people's [12]. Metal exposure, acute and/or chronic has the potentials to induce reproductive and neoplastic damages, via epigenetic changes [13-16] by regulating genome stability, X chromosome inactivation, gene imprinting, and reprogramming gene expression. Metals act as metalloestrogens [17], inhibit DNA repair and alter DNA methylation, change transcriptome and microRNAs production [13], histone acetylation [18] and methylation [19,20] oxidative DNA damage [21] all of which can lead to birth defects, whether translated into mutations or not [21,22].

Some metals can induce sporadic gene mutations because of internal radiation and is unclear the relative relevance of radiation versus chemical activities of DU as a mutagen, while it was shown to induces epigenetic changes via hypomethylation of DNA [20,21,22].

It was not previously attempted to conduct investigation of the association between presentation of BD families and metal load in post-war contexts, while studies of industrial or mine derived metals pollution have implied this correlation. The residential history of the parents, their exposure to major war events, the source of drinking water, all contribute to define the environmental context.

Here we report an observational investigation at Fallujah General Hospital of 56 families with BD and 11 controls inclusive of all the information above, and results of ICP/MS analysis to determine load of ten teratogenic metals in hair of newborns and their parents, with or without BD and of children and adult controls from Italy and Jerusalem.

2. METHODS

Collection of data (Supplementary Fig. 1) was done by medical personnel. Information included reproductive history, information on health of parent's brothers and sisters, historical residence and environmental exposure.

Classification of birth defects was according to definition of the primary phenotype. Patients and controls were taken in order of arrival, among those that accepted in writing to answer to questionnaire, and consenting to the scientific use of data. Pedigrees of families are as standard. Clinical diagnosis was assisted by the use of instrumental diagnosis (Xrays, Echocardiography, CT scans, MRI) as appropriate. Samples of hair of about 2 cm length from the nape of the neck were used for metal load determination by ICP/MS, as recommended by IAEA [12].

Hair samples treatments, digestions and analysis were as reported [23]. XSERIES 2 ICP-MS (Thermo Fisher Scientific, Germany) was used in the standard configuration, with ASX-510 auto-sampler (Cetac, USA). Additional details in supplementary file. For statistics, continuous variables were expressed as median and range, due to their non-normal distribution (assessed by Shapiro-Wilk test) and compared using Mann-Whitney U test. Categorical variables are expressed as percent and compared with Chi-square test for trend. Two-tail P values <0.05 are considered significant.

3. RESULTS

The frequency of birth defects was registered at the Fallujah General Hospital from November 2009 to September 2010. Total number of deliveries were 5896 of which 869 birth defects, with a frequency of 14.7% [24]. In addition, as example, in the month of May 2010 with a total 547 deliveries, there were also 75 premature births of which 60(10.9%) late miscarriages (after 30 weeks) and 10 stillbirths (1.8%).

We classified the BD according to the major primary defect. Many of the BD children show also additional defects in other body compartments, as often the case. The frequency of the different classes of BD in these ten months was: CHD - Congenital heart defects, include ADS, VDS, TOF, 33%; NT-neural tube defects, include anencephaly (possibly underestimated, since it causes miscarriages which can be lost to hospitalization), spina bifida, hydrocephaly, cerebral palsy, 28%; CLP-cleft lip/palate, 14%; "others"-22%. Frequencies of relative prevalence are not significantly different from elsewhere [5,23].

Data collection from 56 families with BD, 31 of them registered in the Hospital for delivery or miscarriage between April and September 2010 and 25 that returned for check up in these months, and from 11 families with a newborn normal child, included reproductive history, health of collateral kin (brothers and sisters) and its progeny, environmental and residential information and was done using the questionnaire in Fig. 1S.

The population studied is highly stable in historic residence and converge to the hospital from different areas of town. The exposure to war chemicals in the environment is reported by subjective record: most of the parents in the study were present at the time of massive attacks to the town in 2004 and/or 2005, cleared rubble, assisted victims and families 116, 119, 120, 132, 142 rebuilt their own house on the remains a bombed one. All mothers declared good to optimum quality of nutrition during pregnancy; most families studied are of large size. These data are shown by examples in Table 1 and in full in Table I 1S for reproductive history of families with BD, Table I 2S for kin and

environmental information of families with BD, and Table I 3S, for pedigrees, kin and environmental information of Iraqi control families. Among the 56 families with BD, 41.36% were CHD, 25.4% NT, 4.7%, CLP, 14.3% Skeletal defects (SK), and 14.3% "others", in similar trend with the prevalence in wider population, above.

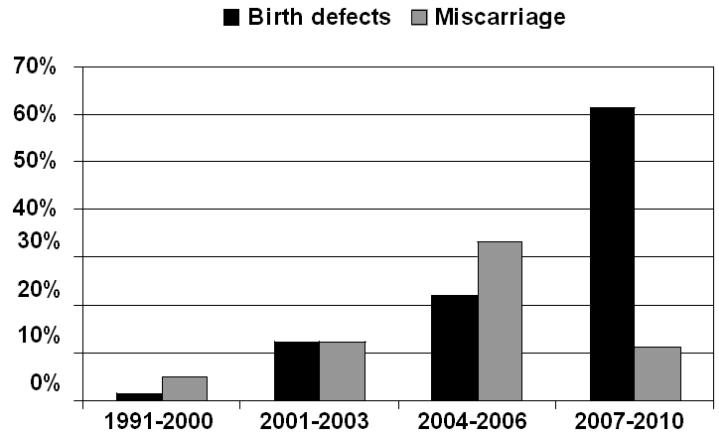

Fig. 1. Prevalence of miscarriage and birth defects in different time periods in Fallujah. p< 0.001 for changes of BD prevalence and p< 0.062 for changes of Miscarriage prevalence

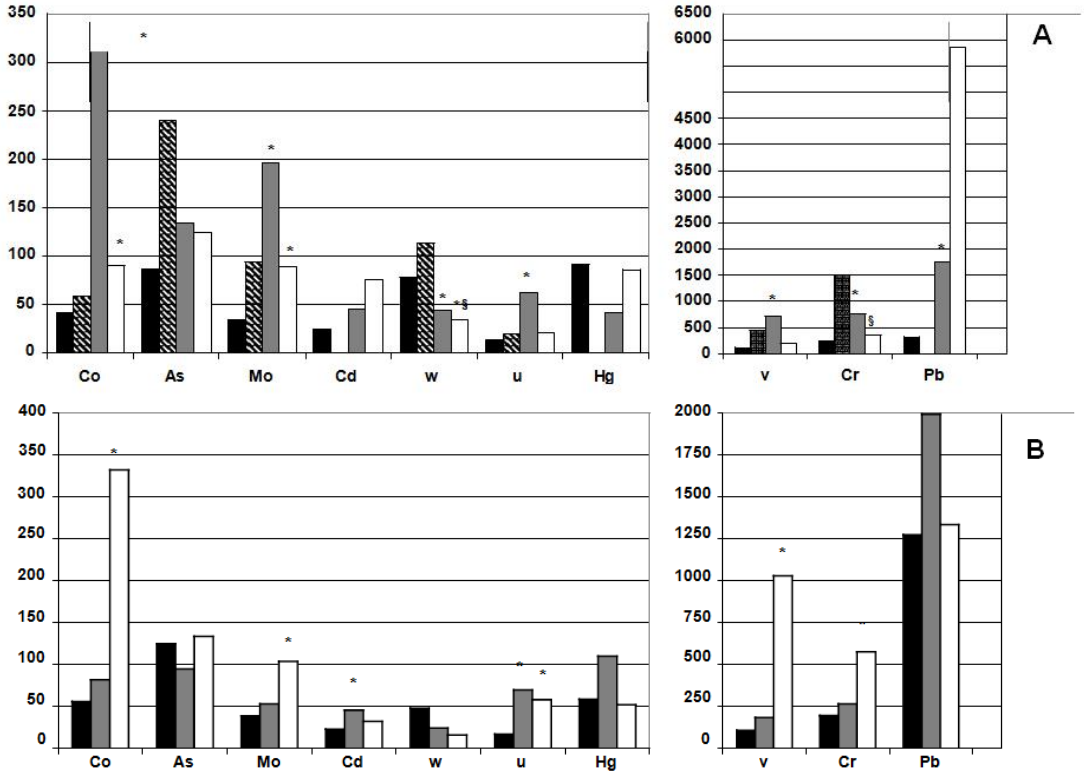

Fig. 2. Hair metal load in ppb, in children (panel A) and in adults (Panel B). Columns correspond to control from Italy (black bars), controls from Jerusalem (dark grey bars), controls from Fallujah (light grey bars) and BD from Fallujah (white bars). * p<0.05 vs controls from Italy; § p<0.05 vs controls from Jerusalem

Table 1A- Birth defects- Family History

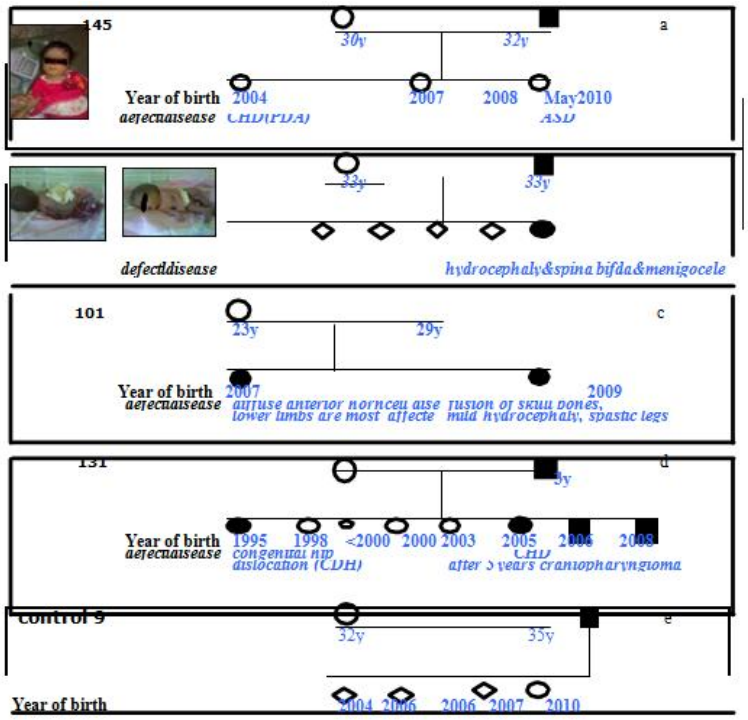

Table 1B –Birth defects- kin and environmental exposure

N/sex/age	BD	House/vicinity		Rescue/ clearing	Acute symptoms	Sibling number	Sibling+progen With BD	Residence2003 /10
		bombed	WP					
145/M/32	CHD-CA	Y2004/N	N	Y				Fallujah,north
145/F/30		Y2004/N	N	Y				Fallujah.north
156/M/33	NT	Y2004/N	N	Y	N	7	11	Fallujah,Nazzal
156/F/33		Y2004/N	N	Y	N	8	4	Fallujah,Alaskari
131/M/42	SK-O	Y2004/N	N	Y	N	3	26	Fallujah,Nazzal
101/F/23	O-NT	Y/Y2004	Y	Y	Y	7	2	Albaghdadi/ 2007 Fallujah, Althubbadh
9/M/35		Y/Y	Y	Y	N	10	25	Fallujah, Alandulus
9/F/32		Y/Y	Y	Y	N	10	1	Fallujah, Alandulus

A-Reproductive history of families;a,b)with birth defect children,born in 2010. C,d)with birth defect children born before 2010.e) heathy child. B-corresponding data on exposure to war events,kin number and health,residence since

empty= healthy

filled in black= birth date

filled in grey= dead

male

female

unknown sex
twins
still born

miscarriage

Table 2. Progeny with BD of families with reproductive history starting before the year 2000

		2007-2010 (3,Sy)			2004-2006 (3y)			2001-2003 (3y)			1991-2000 (10y)		
Code	**Type of BD**	***normal***	***BD***	***MS***	***normal***	***BD***	***MS***	***normal***	***BD***	***MS***	***normal***	***BD***	***MS***
119	CHD&NT		1								4		
131	CDH&CHD	1			1	1		1			2	1	1
134	CHD					1					6		
150	CHD								1		6		
138	CHD		1		3			2			3		
123	NT&NT&NT		1			2					9		
156	NT		1								4		2
139	CHD	3	1		4		1				1		
136	CHD	2	1				2				2		
144	CHD	1	1					3			1		
112	NT		1	2	1		1	1			4		
140	SK		1		1			1			1		
109	CHD & NT		1		1						3		
132	CLP & SK		1	1	2		1	2	1		1		
102	CHD		1				1	2			2		
135	CHD	1	1					1			4		
107	CHD&kidney	2	3		1			1		2	4		
Total		10	16	3	14	4	6	14	2	2	57	1	3
%BD/total births			61,5			22,2			12,5			1,72	
MS/Born				11,5			33,3			12,5			5,1

Families were selected for one BD in their reproductive history after 2003, and because their reproduction spanned from before 2000 up to at least 2006. normal-healthy child; BD-birth defect; MS miscarriage. BD and MS are listed in order of presentation in time in each family: CHD congenital hearth disease, NT neural tube, CLP cleft Lip/Palate, SK skeletal malformation, kidney here stays for atrophic

More than one case of same BD was present in some families: NT in 123 and 105, and CHD in 131 and 145; families 101, 107, 106, 131,132 had children with major defects of different phenotypes. In all of these there was no BD in the immediate kin.

Given to incomplete responses, we have full information only of 50 families on kin, environmental exposure and residence. These include the health state with respect to BD of 552 siblings and 665 progeny (total 1217). The health information is incomplete by defect, since some parents were not informed fully of the health status of all of their kin. Seven cases of birth defects were registered and two infant deaths. These involved 5 families, with families 136 and 138, with CHD children, and a CHD presented in the progeny of the father's siblings, potentially due the presence of a genetic mutation on the father side. Different defects from those in the family of reference were reported in the progeny of the mother's sibling in family 1, and in the progeny of the father's sibling in family 114. For all, the whole extended family resided in the same neighbour, throughout the last 7 years.

Among the 56 families, there are 17 whose reproductive life started since at least 2002 and back up to 1992. The presentation of BD in time increased significantly stepwise during the observation period, from 0.017 in 1991- 2000 to 0.615 in 2007-2010 (Fig. 1 and Table 2). If all the families with one BD in the last 6 years are considered, regardless of the extension backward of their reproductive life, similar results of distribution and same significance ($p<0.001$) for the trend in BD are obtained (supplementary Table II S). The frequency of miscarriages versus births at term also is significantly different, in both cases, comparing these periods of time ($p<0.0062$ for the 17 and $p<0.0003$ for the 56 families, respectively), but has a different pattern than that of BDs. Miscarriages were most frequent in all families in the time interval 2004-2006.

We measured the load of teratogenic/mutagenic metals in the hair of parents and their children with birth defects delivered in Fallujah Hospital between April and September 2010, and of 25 families returning for control visits of children with birth defects born in the last 6 years. We also collected hair samples from 11 families with normal children in the same hospital, from families in Italy and from Arab children in Jerusalem, without familiar records of BD. All participants gave their informed consent to use and delivered the data in scientific study.

Metal concentrations in hair was measured by ICP/MS for ten toxic and carcinogenic metals (V, Cr, Co, As, Mo, Cd, W, U, Hg, Pb) also components of weapons, and are expressed in

ppb, in graphical form in Fig. 2 and in full (supplementary Table III 1S for children and 2S for adults). BD children analyzed were 32 newborn and 13 between 6 months and 7 years of age, for a total of 45. The group of 11 Iraqi children without BD was registered without any selective criteria among the newborns in the period of the study. The group of Italian (from Genoa and Naples, both industrial and traffic polluted large towns) and Jerusalem Arab children, all between 6 months and 7 year of age, were taken randomly among families with no BD. The adults group analyzed include the corresponding parents for BD and all controls (with few exceptions where one of the parent refused to donate or was bold).

While for As and Hg there are no differences in all groups, and W is lower in all Iraqi than outside Iraq controls, the hair metal load in children is significantly higher in control subject from Fallujah than in controls from Ital y for Co, Mo, U, Cr, V and Pb. The same holds true for children with BD from Fallujah relatively to Co, Mo and Pb (Fig. 2, A). Differences in hair metal load is reported for adults in Fig. 2, B. Co, Mo, U, V, and Cr were significantly higher in parents of BD children than in controls from Italy. In addition, Cd and U were also greater in controls from Falluhja with respect to Italian controls. In Fig 1, A, BD children were grouped regardless of their age (newborns and 6 months to 7 years), as there was no significant differences between the two groups in load for any of the ten metals considered (supplementary Table III 1S). Subgroups comparison between CHD and NT children for the load of each of the ten metals, showed no significant differences, suggesting that there is not specific metal association with one kind of these BD (not shown). We left out from the statistical analysis family 119 (Table III, S2), whit a much higher level of all the toxicants that all the other families. This family is one of four in this report living in an house rebuilt on the previous one bombed. Outliners were also observed in other families, being more frequent for Hg and Pb.

In terms of absolute amounts for all elements significantively higher in all the population in Iraq, these are between 2-5 and more in median values than experimental controls, amounts available in the literature, and those previously obtained by our group for another group of ten Italian healthy people of age from 2 to 60 years (not shown).

4. DISCUSSION

In cases where a rapid increase in prevalence of birth defects is suspected/observed, there might be clustering of referrals to the structure where the investigation is undertaken. We have no reason to think that in this case since Fallujah General hospital is the main and the largest public structure in the area, and people convey to it from different areas of town, as shown by the residence of parents. Prenatal diagnosis and therapeutic abortions are not implemented in Fallujah, determining a slight overestimation in comparison with data from countries where these are practiced. Even taking this in consideration, the frequency of BD detected in Fallujah is unusually high compared with those reported in the literature [4,23] usually not exceeding 6%. The data of prevalence are also susceptible of underestimation, due to limited availability of instrumental tools for diagnosis, with possible oversight of minor BD. Nonetheless, the distribution for kinds of different major BD is similar to what reported in the world [4,23].

Modality of the presentation in the families with a BD child is in the majority of cases sporadic and occasional, consistent with the possibility that BD are novel events due to dominant mutation and/or to epigenetic changes during gametogenesis or early embryogenesis. Among the cases where more than one child with BD was born to the same parents, in three cases they differed in phenotypes and there was no BD in the immediate kin. This is most adequately interpreted on the ground of environmental/mother genetic background or epigenetic origin for the multiple events of BD [25,26]. In the few families with recurrence of the same BD in children, two NT and one with two CDH, a supplement of study may be required as to possibility of genetic changes. Similar criteria apply in the cases of occasional recurrence of different or same BD in children in the kin of the family of reference. A persistent environmental effect in the siblings, associated to a generic "predisposition" and same historical residence can explain the recurrences as well as the occurrence of BD with different phenotypes.

The historical reconstruction shows that frequency of BD in the last ten years of the last century was less that 2%, and that of miscarriages about at 5%, similar to that reported for other not heavily industrialized countries. The differences with the past in the

following time windows are highly significant. These also show the different pattern of increase of BD and MS. Miscarriages increase, but with a different pattern than BD and the maximum is coincident with the years of major attacks to the city and decline from 2007, which may suggest that MS are an acute and shorter term response to the environmental changes. For BD, our data do not allow to know if and when the increase will stop and suggest that these are caused by accumulation of the environmental effectors. The fact that the presentation rate of birth defect is not declined in the last years suggest permanence in the environment of teratogenic substances.

Metal load in teratogens (V, Co, Mo, U and Pb) is high in the whole population in Fallujah. If we adopt, as suggested from the sporadic and random presentation of BD the epigenetic paradigm, then this observation, assumes major relevance.

It is known that toxicant metals compared to other known war-contaminants have longer persistence in the environment, accumulate in the organs, act on multiple functions and are capable to induce sporadic epigenetic changes of great impact during gametogenesis and embryo development; interactive effects of multiple metal toxicant were suggested and are still largely undocumented, while is described their capability to unbalance the amounts of essential metals in the organism [25-28]. The toxicants which have increased load in the whole Fallujah population are known for their capability to interfere with embryo development and may be relevant in the induction of MS as acute response, and of BD, as long time effect.

Here we show association of high load of Co, Mo and Pb with all children, Pb being specifically highest in BD children, and of U and V in control Fallujah children. The load of these elements differs from that in adults who all have an U load higher in all controls outside Iraq, and parents of BD children showing Co, Mo, V, and Cr higher than that in all the adults groups. Although the metal load in newborn children hair must derive from mother's exposure, these results show it does not reflects it immediately, suggesting the need of further study on the repartition of the load of different metals during embryo and foetal life, which may be relevant in understanding the mechanisms of metal's teratogenic action. Notwithstanding the low mutagenic performance of teratogenic and carcinogenic metals, their effects are nonetheless important and transmittable to daughter cells within a lineage and transgenerationally in mammals [25-28]. via a mechanistic framework which suggests transmission of epigenetic modifications as a mechanism alternative to germ-line mutagenesis. By their multiple mechanisms of action metals can determine the alteration of functionality of cell lineages, organogenesis and homeostasis in the adult, and the type of cells in the body affected by metals range from somatic cells, also within the developing embryo, to germ cells, both of male and female [29]. The relevance of increase even of moderate amount in teratogenic metal load, and the possible combinatorial effects of their co presence is alluded to in many reports but need further studies to be fully understood.

5. CONCLUSION

We here reported mainly on two aspects related to the birth defects presentation, its frequency, much higher than in the world and of that retrospectively assessed in the place before the 2003 war, and the observational study that indicates that the metal load of Fallujies, in general is unusually high for metals associated with weaponry. That is not enough to establish a cause-effect relationship, but is indicative of muted environmental that can condition differently MS and BD presentation and indicates a path to follow for future studies.

The application of the historical method of recording births gave us a convenient tool for obtaining needed retrospective information and could be implemented for all registrations in countries where registration data have not been recorded in the past.

We hope this knowledge will also help to propose studies directed to the management of the issue along lines of prevention and therapy.

CONSENT AND ETHICAL APPROVAL

As per international standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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