Thyroid Examination in Low-Radiation Exposed Iraqi Clean-up Workers—Immunogenetic Study

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Abstract: Aim: Twenty nine Iraqi cleanup workers at Al-Tuwaitha Research site were examined for the prevalence of thyroid disorders. Materials and Methods: Serological evidence were carried out by measuring the levels of triiodothyronine (T3), thyroxin (T4), thyroid stimulating hormone (TSH) and anti-thyroglobulin (anti-Tg), anti-thyroperoxidase (anti-TPO) auto antibodies. Genotyping for HLA-DRB1 and HLA-DQB1 alleles was done by using the molecular biological technique of polymerase chain reaction-sequence specific oligonucleotide (PCR-SSO). Results: The hormonal study revealed that T4 and T3 levels were below the normal range in five and four workers respectively, TSH was below the normal range in two (7%) workers and elevated in the other three workers (10%). Anti-TPO and anti-Tg antibodies were also determined. The results were positive in 24% and 17% of cleanup workers respectively. Comparison between 16 cleanup workers group A (risk-group), 13 group B (exposed) and 30 (non exposed) control showed that HLA-DQB1*06 allele was significantly $P = 0.01$ lower among group A than controls group. Risk elevation by radiation was most prominent in HLA-DQB1*03, $P = 0.4$ when compared with exposed control. Conclusion: Our data suggest an age-dependent heterogeneity in response to low doses of radiation and the immunogenetic marker such as HLA- DQB1*06 allele may be involved in decreased thyroid disorder risk.

Key words: Thyroid disorders, HLA-DQB1, HLA-DRB1

1. Introduction

The thyroid can be affected by ionizing radiation through the skin by gamma radiation, including X-rays; by fission products, such as cesium; or by ingestion or inhalation of iodine-131 (^{131}I), an isotope present in nuclear fission products. ^{131}I emits mostly beta radiation, which penetrates surfaces more shallowly than gamma radiation [1]. Thyroid affects the adult body's major systems, and crucial to fetal development, its disruption by exogenous chemicals is of intense interest. Moreover, the thyroid, along with breast tissue and bone marrow, are vulnerable to ionizing radiation.

The most common thyroid manifestation of radiation is hypofunction, in addition to thyroid nodules and thyroid cancer. Autoimmune thyroid disease has been linked to therapeutic medical radiation, as well as environmental radiation exposure [2, 3]. Atomic bomb detonations in Japan and nuclear contamination from the Chernobyl Nuclear Power Plant accident were associated with an increased risk of autoimmune thyroid disease [4, 5]. Thyroid disorders seems to have a multifactorial etiology where interactions between the effects of multiple genes and environmental factors are important, and the right combination of genetic, environmental, and endogenous factors is required for the initiation of the disease process [6]. Thyroid disease susceptibility genes include immune-modulating genes,

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such as the major histocompatibility complex, and thyroid-specific genes, including TSH receptors, thyroglobulin and thyroid peroxidase, the anti-thyroglobulin and anti-thyroid peroxidase antibodies belonging to the catalytic type of antibodies destroy the thyrocytes resulting in hypothyroidism. The appearance of anti-thyroid peroxidase antibodies precedes the induction of thyroiditis and the manifestation of hypothyroidism. The auto antigen presentation by major histocompatibility complex molecules is a key point of the autoimmune mechanism [7]. A relationship has been found between autoimmune benign thyroid pathological abnormalities and certain HLA alleles, class II antigens of the human major histocompatibility complex (MHC). The human leukocyte antigens (HLA) DP, DQ and DR, are central elements in the presentation of exogenous antigens to TCD4⁺ lymphocytes and the regulation of immune response [8] and they are characterized by their extraordinary polymorphism [9]. Both class I and II HLA alleles continually provide an updated sample of potential antigens from cytosolic and extracellular compartments to T lymphocytes [10, 11]. Susceptibility to developing these autoimmune diseases is primarily related to certain specific peptides presented by HLA molecules [12, 13]. The aim of the present study is to investigate the impact of exposure to low-dose radiation on thyroid function in sample of Iraqi workers, and the identification of the immuno-genetic markers of the susceptibility to low doses of ionizing radiation, which may predispose individuals under extreme conditions to develop pathological reactions and diseases.

2. Materials and Methods

The study group comprised 29 Iraqi cleanup workers at Al-Tuwaitha Research site (the Iraqi Atomic Energy Commission previously). The mean $\pm$ SD cleanup workers ages was 44 ± 8 years, and all of them (100%) were males, 19 of them with more than ten years of

work at this site demographic and clinical data were recorded. The control group consisted of 30 healthy controls randomly chosen from population living in Baghdad far away from Al-Twaitha nuclear site individuals with negative antithyroid antibodies and no family history of thyroid or other autoimmune diseases.

2.1 Blood Sampling

10 mL of peripheral blood from all select subjects were collected and placed into sterile plain tube. The blood was placed in a cool-box under aseptic conditions and transfer to the laboratory. The serum obtained, through allowing the blood to clot at 37°C for 10-25 minutes before centrifugation, then centrifuged at 3000 rpm for 15 minutes.

T3, T4 and TSH hormones were determined by using VIDAS T3, VIDAS T4 and VIDAS TSH kits (BioMerieux, France) which are enzyme immunoassay for detection of total T3, T4 and TSH in serum using the ELFA technique (enzyme linked fluorescent assay); these systems enable us to estimate total T3, T4, and TSH in serum.

The normal ranges for these thyroid hormones and thyroid antibodies are T4, 60-155 nmol/L; T3, 1.2-2.8 nmol/L; TSH, 0.4-4.0 μ IU/mL.

2.2 Anti TPOAb IgG Estimation

Anti TPOAb IgG were measured using DIALAB assay (enzyme linked immunosorbent assay) for quantitative determination of autoantibodies against Thyroid Peroxidase (TPO) in human serum, DIALAB production and Vertrieb von chemisch Wiener Neudorf Austria.

2.3 Anti TgAb Estimation

Anti TgAb measured using immuno enzymometric assay for quantitative determination of anti-thyroglobulin autoantibodies (TgAb) in human serum or plasma. RADIM S.p.A Roma, Italia. Anti-Tg and anti-TPO positive thyroid autoantibodies were defined as anti-TPO and anti-TG concentrations > 120

IU/mL and > 75 , respectively.

2.4 HLA Typing

For this, a peripheral blood extraction was taken in a tube containing EDTA. The steps for this technique include the QIAamp DNA Mini Kits method genomic DNA purification (QIAGEN 2010). Subsequently, the HLA-DRB1 and HLA-DQB1 alleles were genotyped using polymerase chain reaction and sequence specific oligonucleotide (manufactured by Innogenetics N.V. Technologiepark 6, 9052 Gentm Belgium).

2.5 Ethical Use of Data

Informed consent was obtained from all the study participants, and the guidelines set by the ethics committee of our institute and hospitals were applied.

2.6 Statistical Analyses

The HLA-DRB1 and HLA-DQB1 allele frequencies were estimated by direct counts, and they represent the percentage of individuals who are positive for a particular allele. To compare the differences between the frequencies in the control and clean-up worker groups, a 2×2 contingency table analysis was done

using the Pearson X^2 when the expected value for an HLA marker was less than 5. All of the analyses were performed using the SPSS version 15—software package). The relative risk (RR) was calculated according to the Woolf method. The P values were corrected by multiplying them by the number of alleles tested (Bonferroni correction). The association between the clinical variables and HLA-D alleles was made using the Pearson X^2 test, with the Fisher exact test when the expected value for an HLA marker was less than 5. Only P values of less than 0.05 were considered statistically significant.

3. Results

Clean up workers were divided into two groups (A, B) according to the presence or absence of elevated concentration autoantibodies and/or hormonal disturbance. Group A included (16) cleanup workers (risk group) with increased auto antibodies levels and/or hormonal disturbance, Group B (13) clean up worker without any disturbance (exposed control), clinical characteristics and biochemical measurements of, Groups A and B are shown in Tables 1 and 2. The results revealed that positive TPO autoantibody in 24% (7/29) (mean $\pm$ S.D. 154 IU/mL $\pm$ 102.48, range

Table 1 Characteristics of the 16 clean up worker who tested positive for thyroid auto antibodies and/or hormonal disorder.

Patient No.	Age (yrs)	Period of work	TPOAB (IU/mL)	TGAB (IU/mL)	TSH (μ IU/mL)	T4 (nmol/L)	T3 (nmol/L)
1	38	10	98	13	2.01	66.32	0.84
2	56	32	50	11	0.27	64.05	1.79
3	36	10	103	28	1.21	89.2	1.69
4	40	10	48	39	2.63	60.5	1.09
5	42	17	178	456	1.83	80.52	1.57
6	38	10	37	335	3.03	71.4	2.61
7	32	8	136	11	1.56	80.44	1.93
8	32	10	58	252	2.31	73.01	1.58
9	42	12	49	56	0.31	58.5	0.82
10	54	32	82	22	21.74	46.47	1.45
11	57	32	39	81	2.69	38.55	0.86
12	52	25	31	1451	21.8	30.88	2.3
13	42	17	106	15	1.41	93.46	1.69
14	40	17	375	42	3.1	71.5	2.62
15	35	10	39	81	2.17	38.51	1.52
16	52	25	35	368	7.98	72.06	1.47

Table 2 Characteristics of the 13 decommission workers without any disorder (exposed control).

Patient No	Age (yrs)	Period of work	TPOAb (IU/mL)	TgAb (IU/mL)	TSH (μ IU/mL)	T4 (nmol/L)	T3 (nmol/L)
1	42	17	37	48	2.25	66.02	1.30
2	46	19	39	42	2.09	100	1.78
3	35	10	38	36	1.21	89.27	1.96
4	47	19	50	11	1.58	74.59	1.35
5	55	12	52	10	1.36	83.81	1.80
6	56	27	39	15	1.41	93.46	1.69
7	57	27	51	43	1.42	80.77	1.95
8	47	10	45	10	3.03	65.19	1.76
9	48	26	48	43	0.55	81.3	1.96
10	48	18	39	19	2.2	81.5	1.79
11	43	18	45	10	1.70	67.67	1.77
12	40	10	37	18	4.0	79.21	1.98
13	50	12	33	37	3.3	85.8	1.6

82-375) in one of these, serum TSH was elevated to 21.74 with corresponding change in T4 level in 17% (5/29) out of these cases also had increased anti-TG antibody titers (mean $\pm$ S.D. 456.5 $\pm$ 469.19, range 252-1451) in one of these patient TSH was elevated to 21.8 nmol/L. TSH were below the normal range in two patient (0.27 and 0.31), one of them with T3, T4 below the normal range and were elevated in the other three cases (mean $\pm$ S.D. 17.17 $\pm$ 7.96 range 21.74-7.98), one of them with T4 below the normal range. T4 level were below the normal range in five cases (mean $\pm$ S.D. 42.85 $\pm$ 10.46, range 30.88-58.5), T3 also below the normal range in four cases (mean $\pm$ S.D 0.892 $\pm$ 0.132, range 0.82-1.09) in two of these patients T4 was below the normal range too. Thyroid hormone results associated with clinically observed (hypothyroidism) in two cases, and the presence of sub clinical hypothyroidism in the other cases.

The distribution of HLA-DRB1 and HLA-DQB1 alleles in clean up worker (Group A) and non-exposed controls is shown in Table 3. Investigate that HLA-DRB1*04 alleles shown higher frequencies in healthy control group than patient with odds ratio (OR) = 0.24; and relative risk (RR) = 0.34 but statistically not significant as well as HLA-DRB1*05 which has elevated OR (4.14) and RR (3.75), but it did not reveal any significance. The distribution of the HLA-DQB1*06 allele in group A is significantly less

than in the control group which has 15 alleles (50.0%); $P = 0.001$; Bonferroni-corrected PC = 0.072; RR = 0.250. Thus, the HLA-DQB1*06 allele has an incidence of 50.0% in the control group whereas it occurs in just 12.5% in the Group A. The HLA-DQB1*03 was more frequent in-Group A (13/16, 81.3%) than in Controls (18, 60.0%) $P = 0.4$, OR = 2.889 and RR = 1.354, but the PC value was not statistical significant. In addition the comparison between HLA-DRB1 and HLA-DQB1 alleles in Group A and B revealed that HLA-DRB1*12 was only found in Group B (3, 23.1%), $P = 0.04$ while HLA-DQB1*03 alleles has a lower frequency in-group B (6, 46.2%) than in Group A (13, 81.3%) alleles (13.3%). However, these initially significant differences ($P = 0.04$; OR = 5.05; RR = 1.76) are lost when we apply the Bonferroni correction (PC = 0.288) (Table 4).

4. Discussion

Our work was directed to the identification of the immuno-genetic markers of the susceptibility to low doses of ionizing radiation, which may predispose individual working under extreme conditions to develop pathological reactions and diseases. A cohort of 29 adults cleanup workers 19 of them with more than ten years of work at Al-Tuwaitha nuclear research site were chosen due to the presence of low doses radioactive materials in this region according to the

Table 3 Distribution of HLA-DQB1 and HLA-DRB1 in Group A (risk group) and healthy controls.

Allele	Control Group N = 30		Group A N = 16		OR	RR	P value	Bonferroni-corrected P value
HLA-DRB1	N	PF (%)	N	PF (%)			> 0.05	> 0.05
*01	3	10	4	25.0	3.000	2.500	> 0.05	> 0.05
*02	4	1.3	2	12.5	0.929	2.500	> 0.05	> 0.05
*03	5	16.7	3	18.8	1.154	1.125	> 0.05	> 0.05
*04	11	36.7	2	12.5	0.247	0.341	> 0.05	> 0.05
*05	1	3.3	2	12.5	4.143	3.750	> 0.05	> 0.05
*06	1	3.3	0	0	0	0	> 0.05	> 0.05
*07	6	20.0	6	37.5	2.400	1.875	> 0.05	> 0.05
*08	1	3.3	0	0	0	0	> 0.05	> 0.05
*11	6	20.0	6	37.5	2.400	1.875	> 0.05	> 0.05
*13	5	16.7	6	37.5	3.000	2.250	> 0.05	> 0.05
*14	4	13.3	5	31.3	2.955	2.344	> 0.05	> 0.05
*15	9	30.0	3	18.8	0.538	0.625	> 0.05	> 0.05
*16	3	10.0	2	12.5	1.286	1.250	> 0.05	> 0.05
HLA-DQB1								
*02	11	36.7	8	50	1.727	1.364	> 0.05	> 0.05
*03	18	60.0	13	81.3	2.889	1.354	> 0.05	> 0.05
*04	2	6.7	1	6.3	0.933	0.938	> 0.05	> 0.05
*05	9	30.0	7	43.8	1.815	1.458	> 0.05	> 0.05
*06	15	50.0	2	12.5	0.143	0.250	0.012	0.072

PF phenotype frequency; Group A clean up worker with high concentration autoantibodies and hormonal disturbance.

Table 4 Distribution of HLA-DQB1 and HLA-DRB1 in Group A (risk group) and Group B according to the presence or absence of high concentration auto antibodies and hormonal disturbance.

Allele	Group A N = 16		Group B N = 13		OR	RR	P value	Bonferroni-Corrected P Value
HLA-DRB1	N	PF (%)	N	PF (%)				
*01	4	25.0	3	23.1	1.111	1.083	> 0.05	> 0.05
*02	1	6.3	0	0	0	0	> 0.05	> 0.05
*03	3	18.8	2	15.4	1.269	1.219	> 0.05	> 0.05
*04	2	12.5	3	23.1	0.476	0.542	> 0.05	> 0.05
*05	2	12.5	1	7.7	1.714	1.625	> 0.05	> 0.05
*07	6	37.5	4	30.8	1.350	1.219	> 0.05	> 0.05
*11	6	37.5	3	23.1	2.000	1.625	> 0.05	> 0.05
*12	0	0	3	23.1	0	0	0.042	> 0.05
*13	6	37.5	5	38.5	.960	0.957	> 0.05	> 0.05
*14	5	31.3	3	23.1	1.515	1.354	> 0.05	> 0.05
*15	3	18.8	2	15.4	1.269	1.219	> 0.05	> 0.05
*16	2	12.5	2	15.4	0.786	0.813	> 0.05	> 0.05
HLA-DQB1								
*02	8	50	7	53.8	0.857	0.929	> 0.05	> 0.05
*03	13	81.3	6	46.2	5.05	1.760	0.04	0.288
*04	1	6.3	1	7.7	0.800	0.813	> 0.05	> 0.05
*05	7	43.8	5	38.5	1.244	1.138	> 0.05	> 0.05
*06	2	12.5	5	38.5	0.229	0.325	> 0.05	> 0.05

Group B clean up worker without any disturbance (exposed control).

study of detection of radiological and chemical of public exposure to uranium-235 at that site [14, 15]. Serological evidence of thyroid disorders among them were investigate that there was heterogeneity in response to low doses of radiation dependant on age and period of work at Al-Tuwaittha nuclear research site. Thyroid hormone results associated with clinically observed (hypothyroidism) in two cases, with hormonal disturbance results suggest the presence of sub clinical hypothyroidism. Researchers interested in the study of correlation of TSH, T4, and T3 levels and thyroid disorders, they usually found TSH levels in hypothyroidism were more than normal range [16, 17]. Guth et al. [18] were reported that the goiter depending on the resultant changes in T4 and T3. Some other researchers also found that the T4 level increased in thyroid toxic goiter [19]. It is well known that exposure to ionize radiation is associated with an increase in incidence of thyroid abnormalities and in particular thyroid cancer [20-22]. An increase in the incidence of thyroid cancer was observed in survivors of the atomic bomb in Japan [23] and in residents of the Marshall Islands exposed to ionize radiation during the testing of hydrogen bombs [24]. Of note is the higher rate of thyroid cancer in females. The cohort addressed in our study mostly comprised men therefore reducing the likelihood of thyroid cancer per se. Thyroid antibodies are reliable markers of thyroid autoimmunity and surrogates of subsequent thyroid dysfunction [25, 26]. The autoimmune process detected by the presence of these auto antibodies was in most cases, in its early sub clinical phase and had not progressed close to the presentation of clinical disease, because only three (27%) of the 11 autoantibody positive cases had increased TSH levels and two had been diagnosed with hypothyreosis. Men compose all cases in this study where in the age (30-57) the production of anti TPO antibodies is inheritable in an autosomal fashion in women but not in men [27]. In adults, unlike in children, other radiation-induced pathologies of the thyroid gland such as autoimmune thyroiditis may

become more prevalent. In atomic bomb survivors and patients treated with external radiation for non-thyroid diseases, exposure to radiation was associated with increased incidence of thyroid autoimmunity [28-30]. However, it is important to acknowledge that thyroid autoimmunity has also been described in healthy individuals with no documented exposure to ionizing radiation. In two population-based studies from the United Kingdom (Wickham Study) and Australia (Busselton Health Survey) anti-TPO prevalence rates of 6.8% and 6.6% respectively, were reported [31, 32]. To investigate the combined influence of HLA-DRB1 and HLA-DQB1 alleles on sensitivity of cleanup workers were divided into two groups (A and B) according to the presence or absence of auto antibodies and/or hormonal disturbance. The effect of radiation exposure on clean up worker susceptibility to thyroid disorder based on HLA class II (HLA-DRB1, HLA-DQB1) polymorphisms. HLA genotype distribution among the controls—non exposed to radiation was almost identical to that in Group B (exposed control) cleanup workers. Genotyping of HLA-DRB1 and HLA-DQB1 alleles in Group A and apparently healthy controls showed that HLA-DRB1*05 which has elevated OR (4.14) and RR (3.75), this means that the individuals with this above allele have 4.14 times greater chance of predispose to thyroid disorder than those of the same population who lack it. This result is similar with other studies by Bogner et al. [33] and Parkes et al. [34] which revealed that HLA-DR5 has been associated with thyroid disorders such as hashimoto thyroiditis, postpartum and non goitrous autoimmune thyroiditis. On the other hand the distribution of the HLA- DQB1*06 allele in group A is significantly $P = 0.012$ less than in the control group (15 alleles) (50.0%); Bonferroni-corrected $P = 0.072$; RR = 0.250). Thus, the HLA-DQB1*06 allele has an incidence of 50.0% in the control group whereas it occurs in just 12.5% in-group A. These results suggest that the HLA-DQB1*06 allele can provide a protective effect against

thyroid disorder in non exposed individual a protective effect has also been proposed by Tamai et al. [35] in a Japanese cohort of 105 HT patients and 317 control subjects for DQA1*0102 (RR = 0.3) and DQB1*0602 (RR = 0.1). The distribution of HLADRB1 and HLA-DQB1 alleles in groups A and B revealed that risk elevation by radiation was most prominent in HLA-DQB1*03 alleles which has a higher frequency in group A (13, 81.3%) than in the group B (6, 46.2%), these types of associations have been described principally in Graves's disease and hashimoto thyroiditis [12, 36, 37]. The HLA-DR3 allele has been associated with both of these diseases, however, these initially significant differences ($P = 0.04$; OR = 5.05) are lost when we apply the Bonferroni correction $P = (0.288)$. Our findings may have been influenced by the small number of patients in this study. HLA-antigens are probably involved in the pathology of many diseases. This associations has recently been estimated and documented. Thus, when we know a person's set of HLA-antigens we can predict the probability of the development of certain pathological processes, the susceptibility to specific harmful factors, medicines, etc. [38]. These results suggested that HLA-DQB1*06 allele may be involved in decreased thyroid disorder risk among non-exposed people while risk elevation by radiation was most prominent in HLA-DQB1*03 alleles compared with other genotype. Therefore, in accordance with published data, and due to the high susceptibility of the thyroid gland to radiation damage, a detailed long-term follow-up of thyroid function during the next several decades would be of great importance in identifying thyroid malignancies and deviation of its function in Iraqi clean-up workers.

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