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Gene Polymorphisms of Cytokines IFN γ $^{+874}$ (A/T), TNF A $^{-308}$ (G/A), IL-6 $^{-174}$ (G/C), L'il-10 $^{-1082}$ (A/G), $^{-819}$ (C/T) $^{-592}$ (C/A), TGF-β1 $^{+869}$ (T /C), $^{+915}$ (G/C) in Algerian Type 1 Diabetes and Latent Autoimmune Diabetes in Adults (LADA)

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Abstract

Background: We aimed to investigate the association between five cytokines (IFN γ $^{+874}$ (A/T), TNF α^{-308} (G/A), IL-6 $^{-174}$ G/C, l'IL-10 $^{-1082}$ A/G, $^{-819}$ (C/T) $^{-592}$ C/A), TGF-β1 $^{+869}$ (T/C), $^{+915}$ (G/C) and patients with type 1 diabetes (T1D) and Latent Autoimmune Diabetes in Adults (LADA).

Methods: Polymorphisms of cytokine were determined using the Sequence Specific Primers method (PCR-SSP) in 50 patients and 74 controls.

Results: The results showed significantly higher frequency of IFN γ $^{+874}$ TA genotype (65.38% *vs*. 45.95%, *pc* = 0.046) in T1D vs. controls. While T allele (56.25% *vs*. 35.14%) in LADA *vs*. controls. While significantly higher frequency of TNFα ($^{-308}$G/A) A allele (26.92% *vs*. 13.51%) in T1D *vs*. controls and significantly higher frequency of GA Genotype (41.6% *vs*. 24.32%) in LADA *vs*. controls. While the results showed significantly higher frequency of IL-10 $^{-1082}$ A/G) G/A genotype (65. 38% *vs*. 45.95) in T1D and LADA versus control and IL-10 $^{-592}$ (C/A) C allele (84% *vs*. 68.92%) Regarding polymorphisms of IL-6 no significant difference was observed between T1D, LADA and controls.

Conclusion: These results suggest that the secretion low of IFN-γ and high secretion of TNF- α may play an important role in protection and susceptibility to autoimmune diabetes in the Algerian population.

Abbreviations: IFNγ: Interferon Gamma; TNFα: Tumor Necrosis Factor Alpha; IL-6: Interleukin 6, l'IL-10: Interleukin 10, TGF-β1: Transforming Growth Factor Beta, T1D: Type 1 diabetes, LADA: Latent Autoimmune Diabetes in Adults (LADA), PCR-SSP: Polymeras Chain Reaction Sequence Specific Primers, DNA: Deoxyribonucleic Acid.

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Keywords: Type 1 diabetes; Latent autoimmune diabetes in adults; Cytokines

Introduction

Type 1diabetes (T1D) is a chronic autoimmune disease characterized by absolute insulin deficiency resulting from the progressive immune-mediated destruction of pancreatic islet β cells[1,2]. Genetic factor influence both susceptibility and resistance to the disease. More than 20 loci involved in susceptibility to type 1 diabetes have been described among them IDDM1 (Major his-

tocompatibility Complexe-MHC)[3], IDDM2-Insuline gene on chromosome[4] and the PTPN22 gene[5].

The patients with Latent Autoimmune Diabetes In Adults (LADA) have a progressive insulin secretion defect and have a genetic predisposition with type 1 diabetes (1) but differed phenotypically from type 1 diabetes diagnosed after age 35 years and within LADA depended on GAD antibody (GADA) levels. Multiple immune mediators are implicated in the destruction or protection of the pancreatic β-cells including tumor necrosis factor (TNFα), interferon (IFNγ) and IL-6. They are pro-inflammatory cytokines produced primarily by activated macrophages that infiltrate the islets during the pathogenesis of diabetes[6] and play a central role in β-cell destruction[7].

In human, the IFN γ is encoded by four-exon gene on chromosome 12q14, also exhibits antiviral activity but in contrast to the type I interferon, its main biological activity appears to be immunomodulatory[8]. The TNF-α gene is located within the highly polymorphic major histocompatibility complex region on chromosome 6p21.3[9]. Many studies have shown that SNP at position $^{-308}$ G/A was associated with various inflammatory conditions. Polymorphism in the 50 flanking region of the IL-6 gene on chromosome 7p21 at position -174 has been reported to exert an effect on its secretion and function[10]. Interleukin-10 (IL-10) is an anti-inflammatory cytokine with a crucial role in preventing inflammatory and autoimmune pathologies[11]. IL-10 is immunosuppressive substance produced within the body and plays a role in the regulation of immune responses[12]. The gene for IL-10 in chromosome region 1q31– q32 presents two CA-repeat microsatellites in the 50-flanking region: IL-10 R and IL-10 G, at _4 and _1.1 kb, respectively[13]. In addition, three single nucleotide polymorphisms (SNPs) in its promoter at positions $^{-1082}$ (G/A), $^{-819}$ (C/T) and $^{-592}$ (C/A) have been identified[14].

Single nucleotide polymorphisms (SNPs) of IFNγ, TNFα, IL-6, l'IL-10, TGF-β1 may influence the expression of the coded cytokine and in this way these candidate genes may play a role in the patho-mechanism of T1DM and LADA. In our study we aimed to determine the genotype association of IFN γ $^{+874}$ (A/T), TNF α^{-308} (G/A), IL-6 $^{-174}$ G/C, l'IL-10 $^{-1082}$ A/G, $^{-819}$ (C/T) $^{-592}$ C/A), TGF-β1 $^{+869}$ (T/C), $^{+915}$ (G/C) SNP in Algerian case with type 1 diabetes in juvenile and Latent Autoimmune Diabetes in Adults.

Methods

Patients and Controls

Blood samples were taken from 24 juveniles with T1D (18 - 35 years) and 26 LADA treated in the First service of diabetology, Mustapha University, Alger during 2010 - 2014 and 74 (18 - 35 years) of unrelated healthy individuals used as a control. Diabetic patients were diagnosed using the criteria of the National Diabetes Data Group[15]. The diagnosis of Type 1 diabetes and LADA was based on clinical data consisting of diabetic ketoacidosis, absolute insulin dependence and /or spontaneous ketoacidosis and /or severe insulinopenia and weight loss.

Cytokine gene polymorphism genomic DNA was isolated from peripheral blood samples using phenol-chloroform technique[16]. 50 patients with auto immune and 75 normal healthy controls were studied for cytokine gene polymorphisms using the Polymerase chain reaction–sequence specific primers (PCR-SSP). The polymorphisms analyzed were interferon-γ (IFN γ)(A^{+874} T), TNF α (G $^{-308}$ A), interleukin IL-6 (G $^{-174}$ C), IL-10 (A $^{-1082}$ G, T $^{-819}$ C, C $^{-592}$ A) and transforming growth factor TGF-β1 (T $^{+869}$ C), (G $^{+915}$ C) (One Lambda Canoga Park CA). All PCR amplifications were performed in 10 µl reaction volumes containing 80 ng/µl of genomic DNA mixed with master mix containing 2U/µl Taq DNA polymerase. This DNA and master-mix was dispensed into 96-well trays pre-aliquoted with primers and amplified in an automated thermal cycler (9600 Perkin-Elmer –Cetus, CA, USA). The PCR products were fractionated on 2% (w/v) agarose gel electrophoresis, stained with ethidium bromide (10 µg/ml) and visualized under UV illumination. Each tube had an internal positive control band to check the integrity of PCR.

Statistical analysis

Statistical analysis was performed using the compare 2 software, version 2 (Chicago, IL, USA). Fisher's exact test was used to determine the significance of differences between the patient and the control groups. Bonferroni's correction was performed for multiple comparisons. Odds ratios were calculated using Woolf's method with Haldane' modification whenever the numbers were five or less[17] table 1.

Table 1 : IFN γ $^{+874}$ (A/T), TNF α^{-308} (G/A), IL-6 $^{-174}$ G/C, l'IL-10 $^{-1082}$ A/G, -819 (C/T) $^{-592}$ C/A), TGF-β1 $^{+869}$ (T/C), $^{+915}$ (G/C) genotype frequencies among cases with type 1 diabetes compared to controls with their statistical significance.

Genotype/	T1D N= 26				LADA N= 24				Control N= 74 n(%)
	n(%)	Pc	OR	(95%CI)	n(%)	Pc	OR	(95%CI)	
IFN γ $^{+874}$ (A/T)									
AA TA TT	8 (30.76) 17 (65.38) 1 (3.84)	0.169 0.046 0.153	0.62 2.22 0.29	(-) 0.80 - 6.39 -	4(16.66) 14(58.33) 6 (25)	0.013 0.149 0.062	0.28 - -	0.06 - 0.95 0.58 - 4,7 0.61 - 8,72	31(41.89) 34(45.33) 9(12.16)
TNF α $^{-308}$ (G/A)									
GG GA AA	14 (53,84) 10 (38,46) 2 (7,69)	0,027 0,082 0,05	0,40 1,94 6,08	0,14 - 1,14 - 0,29 - 363,6	14 (58,3) 10 (41.6) 0	0,06 0.05 /	0,48 2.22 /	- 0.73 - 6.46 /	55(74,32) 18(24,32) 1(1,35)
IL-6 $^{-174}$ (G/C)									
GG GC CC	16 (61,538) 8 (30,76) 2 (7,69)	0,105 0,243 0,056	0,55 1,38 6,08	- - -	19(79,1) 5 (20,8) 0	0,352 0,403 /	1,31 0,82 /	- - /	55(74,32) 18(24,32) 1(1,35)
IL-10 $^{-1082}$ A/G									
AA GA GG	7 (26.92) 17 (65.38) 2 (7.69)	0.24 0.046 0.11	0,68 2 .22 0,36	 - -	5 (20,8) 14(58,3) 5 (20,8)	0,10 0,149 0,376	0,49 1,65 1,13	- - -	26(35,14) 34(45.95) 14(18,92)
IL-10 $^{-819}$ (C/T)									
CC CT TT	12 (46,16) 13 (50) 1 (3,84)	0,46 0,27 0,25	0,96 1,31 0,38	- - -	16(66,6) 8(33,33) 0	0,05 0,20 /	2,23 0,66 /	- - /	35(47,30) 32(43,24) 7(9,46)
IL-10 $^{-592}$ (C/A)									
CC CA AA	12 (46,15) 13 (50) 1 (3,84)	0,46 0,27 0,25	0.86 1.31 0.38	- - -	16(33) 8 (33) 0	0,207 0,207 /	0,66 0,66 /	- - /	35(47,30) 32(43,24) 7(9,46)
TGFβ1 $^{+869}$ T/C									
TT TC CC	13 (50) 10 (38,46) 3 (11.53)	6.8 10^{-3} 5.8 10^{-3} 0.322	3.35 0.30 1.25	- - -	8 (33,33) 12 (50) 4 (16,66)	0,146 0,061 0,144	1,68 0,48 1,91	- - -	17(22,97) 50(67,57) 7(9,46)
TGFβ1 $^{+915}$ (G/C)									
GG GC CC	16(61,53) 10 38,46) 0	1.310^{-3} 1.310^{-3} /	0,19 5,16	- -	19 (79,1) 5 (20,83) 0	0,09 0,09	0,46 2,17	- -	66(89,19) 8 (10,81) 0

R (95th CI) ¼ odds ratio (95% confidence interval) NB:

Results

Table 2 and table 3 shows TNF, IFNγ, IL-6, IL10 and TGF genotype and allele distribution in our T1D, LADA population and controls. IFN γ $^{+874}$ TA genotype was significantly more frequent in T1D patients than in the controls (65.38% *vs.* 45.95%, pc = 0.046, OR = 2.22) corresponding to a profile of intermediary secretion (73.07% *vs.* 45.95%, *pc* = 0.009, OR = 3.19) and T allele was significantly more frequent in LADA patients than in the controls (56.25% *vs.* 35.14%, *pc* = 0.005, OR = 2.37) corresponding to a profile of high secretion (29.16% *vs.* 12.16%, *pc* = 0.027, OR = 2.97). While A allele (64.86% *vs.* 43.75%, *pc* = 0.005, OR = 0.42) and AA genotype (41.89% *vs.* 16.66%, *pc* = 0.013, OR = 0.28) respectively were significantly more frequent in control than in LADA patient, corresponding to a profile of low secretion (41.89% *vs.* 16.66%, *pc* = 0.013, OR = 0.28). While significantly, higher frequency of TNF α^{-308} A allele have obtained in T1D *vs.* Control (26.92% *vs.* 13.51%, *P* = 0,015, OR = 2.36) corresponding to a higher secretion profile (46.15% *vs.* 25.68%, *P* = 0.027, OR = 2.48) in T1D versus controls. However the results showed significantly higher frequency of TNF α ($^{-308}$G/A) GA Genotype (41.6% *vs.* 24.32%, *P* = 0.05, OR =2.22) and high secretion profile (45.83% *vs.* 25.68%, *pc* = 0.032, OR = 2.45) in LADA versus controls. However the results showed significantly higher frequencies of TNF α^{-308} G allele 86,49% *vs.* 73,07%, *pc* = 0.015, OR = 0.42) GG genotype (74.32% *vs.* 53.84%, *pc* = 0.027, OR = 0.4) in controls versus T1D, corresponding to a profile of low secretion (53.85 % *vs.* 74.32%, *pc* = 0.027, OR = 0.4).

Table 2 : IFN γ $^{+874}$ (A/T), TNF α^{-308} (G/A), IL-6 $^{-174}$ G/C, l'IL-10 $^{-1082}$ (A/G), $^{-819}$ (C/T) $^{-592}$ C/A), TGF-β1 $^{+869}$ (T/C), $^{+915}$ (G/C) allele frequencies among cases with type 1 diabetes and LADA compared to controls with their statistical significance

Alleles	T1D 2N= 52				LADA 2N= 48				Control n(%) 2N= 148
	n(%)	Pc	OR	(95%CI)	n(%)	Pc	OR	(95%CI)	
IFN γ $^{+874}$ (A/T)									
A **T**	33 (63.46) 19 (36.53)	0.417 0.417	0.94 1.06	(-) (-)	21(43,75) 27(56,25)	5.1 10^{-3} 0 .05	0.42 2.37	0.20 - 0,86 1.16 - 4.87	96(64.86) 52(35.14)
TNF α^{-308} (G/A)									
G **A**	38 (73.07) 14 (26.92)	0.015 0.015	0.42 2.36	(0.18 - 1.004) (0.99 - 5.43)	38(79,16) 10(20,83)	0,10 0,10	0,59 1,68	- -	128(86.49) 20(13.51)
IL-6 $^{-174}$ (G/C)									
G **C**	40 (76,923) 12 (23,077)	0,051 0,051	0,52 1,92	(-) (-)	43(86,5) 5 (10,4)	0,334 0,334	1,34 0,74	- -	128(86,49) 20(13,51)
IL-10 $^{-1082}$ A/G									
A **G**	31 (59,61) 21 (40,38)	0,43 0,43	1,06 0,94	(-) (-)	24 (50) 24(50)	0,16 0,16	0,72 1,39	- -	86(58,11) 62(41,89)
IL-10 $^{-819}$ (C/T)									
C **T**	37 (71,16) 15 (28,84)	0,39 0,39	1,11 0,90	(-) (-)	40(83,3) 8 (16,6)	0,02 0,044	2,25 0,44	- -	102(68,92) 46(31,08)
IL-10 $^{-592}$ (C/A)									
C **A**	37 (71,15) 15 (28,84)	0.39 0,39	1,11 3,27	(-) (-)	40(84) 8 (16)	0.03 0.03	2.25 0. 44	- -	102(68.92) 46(31.08)
TGFβ1 $^{+869}$ T/C									
T **C**	36 (69,23) 16 (30,76)	0,058 0,058	1,71 0,58	(-) (-)	28(58,3) 20 (41,6)	0,43 0,43	1,07 0,94	- -	84(56,7) 64(43,24)
TGFβ1 $^{+915}$ (G/C)									
G **C**	42 (80,76) 10 (19,23)	2.1 10^{-3} 2.1 10^{-3}	0,24 4,17	(-) (-)	43 (89,6) 5 (10,41)	0,09 0,09	0,49 2,03	- -	140(94,59) 8(5,41)

OR (95th CI) ¼ odds ratio (95% confidence interval)

Table 3: IFN γ $^{+874}$ (A/T), TNF α^{-308} (G/A), IL-6 $^{-174}$ G/C, l'IL-10 $^{-1082}$ A/G, $^{-819}$ (C/T) $^{-592}$ C/A), TGF-β1 $^{+869}$ (T/C), $^{+915}$ (G/C) Secretion profil among cases with type 1 diabetes compared to controls with their statistical significance.

Secretion profile	T1D N = 26 2N = 52				LADA N = 24 2N = 52				Control n(%) 2N= 148
	n(%)	Pc	OR	(95%CI)	n(%)	Pc	OR	(95%CI)	
IFN γ $^{+874}$ (A/T)									
High **Intermédiate** **Low**	0(0) 19 (73,07) 7 (26,92)	- 0,009 0,095	- 3,19 0,51	- 1,10 - 10,008 -	7 (29,16) 13(54,16) 4 (16,66)	0,027 0,244 0,013	2,97 1,39 0,28	0,80 - 10,41 - 0,063 - 0,95	9(12,16) 34(45,94) 31(41,89)
TNF α^{-308} (G/A),									
High **Low**	12 (46.15) 14 (53.85)	0 .027 0.027	2.48 0.40	0.87 - 6.92 0.14 - 1.14	11(45.83) 13(54.16)	0 .032 0.032	2.45 0,41	0,83 - 7.05 0,14 - 1.20	19(25.68) 55(74.32)
IL-6 $^{-174}$ G/C									
High **Low**	24 (92,30) 2 (7,7)	0,056 0,056	0,16 6,08	- -	24 (100) 0	0,561 /	∞ /	- /	73(98,65) 1(1,35)
IL10									
High **Low** **Intermediate**	2 (7.69) 7 (26.93) 17 (65.38)	0.003 0.048 9.6.10^{-6}	0.15 0 .43 8.10	- - -	5 (20.8) 4 (16.7) 15(62.5)	0,106 0,292 4.4.10^{-4}	0,49 0,67 7,14	- - -	26(35.14) 34(45.95) 14(18.92)
TGF-β1									
Low **Intermediate** **High**	1 (3.846) 10 (38.462) 15 (57.692)	1.410^{-13} 4.010^{-6} 2.010^{-5}	0,01 22,50 7,81	0.000 - 0.065 4.052 - 220.742 2.544 - 24.136	2 (8.333) 5 (20.833) 17 (70.833)	0 0.003 0	0,02 9,74 13,91	0.002 - 0.099 1.376 - 103.584 4.167 - 48.219	61(82,43) 2(2,7) 11(14,86)

While the results showed significantly higher frequency respectively in T1D and LADA versus control for IL-10 $^{-1082}$ A/G) G/A genotype (65. 38% *vs.* 45.95, *Pc* = 0.046, OR = 2.22) and IL-10 $^{-592}$ (C/A) C allele (84% *vs.* 68.92%. *Pc* = 0.03, OR = 2.24) with intermediated profile (65.38% *vs.* 18.92 % Pc = 9.6.10^{-6} OR = 8.10), (62.5% *vs.* 18.92 % *Pc* = 4.4.10^{-6} OR = 7.14) and the results showed significantly higher frequency of TGF-β1 $^{+869}$ TT genotype (50% *vs.* 22.97%, *Pc* = 6.8 10^{-3}, OR = 3.36) and low secretion profile (45.83% *vs.* 25.68%, *pc* = 0.032, OR = 2.45) only in T1D vs. controls. The variants of interleukin IL-6 $^{-174}$ G/C, l'IL-10 $^{-819}$, TGF-β1^{+915}(G/C) polymorphic genotypes or alleles ($P > 0.05$) did not show a significant difference between patients and controls.

Discussion

In our study, we investigated the association between the T1DM and of IFN γ $^{+874}$ (A/T), TNF α^{-308}(G/A), IL-6 $^{-174}$ G/C, l'IL-10 $^{-1082}$ A/G, $^{-819}$ (C/T) $^{-592}$ C/A), TGF-β1 $^{+869}$ (T/C) $^{+915}$ polymorphisms in T1D and LADA . Our results indicate that the of IFN γ $^{+874}$ T allele and of TNFα^{-308} A allele are associated with a T1D and LADA.

The polymorphism effects of TNFα and TNFβ on the risk of T1D have been reported in several other studies[18,19]. In the Korean population suggested that genetic effects of TNF gene polymorphisms on the risk of T1D might not be totally dependent on HLA genes[20]. We especially focused on TNFα^{-308} (G/A), which is particularly interesting because of its known involvement in the differential transcriptional activator[21]. Also the aberrant expression of MHC class II molecules by non-immune cells has been described in patients with in T1D patients on pancreatic cells[22,23]. IFN-γ can induce the aberrant expression of HLA-DR as well as DP and DQ antigens on thyrocytes *in vitro* and human pancreatic islet cells[24,25]. IFN-γ, are also able to induce MHC antigen up-regulation and the expression of adhesion molecules by target cells, which overall can promote the activation of an autoimmune response[26]. Similar results have been reported from patients with T1D of Hungarian origin and Latvians[27,28]. We suppose that in these cases, higher TNF α production associated with the position $^{-308}$ G/A genotype in Langerhans islets, suggests that the autoimmune Th1 responses in T1D are probably TNF- α mediated and low production in control have a protective effect against the autoimmune process and might delay the destruction of the b-cells.

We found no significant difference in IL-6 $^{-174}$ G/C frequency between patients and their healthy control counter parts. This can be translated as an absence of association of IL-6 $^{-174}$ G/C polymorphism to Algerian T1D and LADA patients. Our result is in total contrast with previous reports. In fact, a higher prevalence of IL-6 $^{-174}$ GG genotype was reported in UK Caucasoid T1D patients[29]. In another study of Danish T1D families, IL-6 $^{-174}$ C allele was associated with T1D only in females[30]. Herman et al (2005) reported that IL-6^{-174} G was associated with older age onset of T1D in the presence of high cytokine producer IL-1β and TNF-α genotypes[31].

We have found significant difference of genotype and alleles frequencies among T1D and LADA respectively compared to controls for gene polymorphism at position l'IL-10^{-1082} and l'IL-10^{-592} (C/T). Our results agreement with that reported by Reynier et al. with lack of association of IL-10 promoter gene variants with type 1 diabetes in a French population and Urcelay and al in Spanish population[32,33]. The frequency of low producer haplotype of IL-10 ATA haplotype with positions^{-1082}(A/G), $^{-819}$ (C/T)$^{-592}$ (C/A) has been shown to be increased in the patients with adult-onset diabetes in Japan[34]. IL-10 has been shown to hyperinduce ICAM-1 expression on vascular endothelium where pancreatic and to drive pathogenic autoimmune responses and accelerated diabetes through an ICAM-1-dependent pathway[35].

Regarding TGF-β1 gene no significant difference was observed between LADA patients and controls position $^{+869}$ (T/C), $^{+915}$ (G/C). Kumar et al. 2007 demonstrated that a significant increase in high producer haplotypes of TGF- β1 with TNF α^{-308} GA/AA in the patients with T1D compared with the controls were observed[36]. The TGF- β1 has been shown to be an extremely potent chemotactic factor *in vitro*, which influences monocyte recruitment and accumulation by increased expression of α and β-integrins[37]. Increased levels of TGF- β1 have been associated with destruction of pancreatic beta cells and pathogenesis of diabetic complications[38]. Hence, in the presence of high secretors of TNF-α, the high secretor genotypes of TGF- β1 may have a role both in destruction of pancreatic beta cells and in migration of CD4+ and CD8+ T cells into the pancreas[39].

Conclusions

We conclude that additional genetic predisposition to T1D and LADA; these results suggest that the secretion low of IFN-γ and high secretion of TNF-α may play an important role in protection and susceptibility to autoimmune diabetes in the Algerian population. Because TNF-α, IFN γ and IL10 showed a significant association with T1D and LADA, we wanted to study whether simultaneous presence of TNF-α genotypes with different genotypes of the other cytokines in an individual could suggest an interaction between these cytokine genes.

Authors' contributions

RR, AH, EM, conceived and designed the study and collected the data, MA, AB selection of patients, CTB, MCA and NA wrote the manuscript. All authors read and approved the final manuscript.

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Competing Interests: The authors declare that they have no competing interests. Availability of data and materials. The data used in the analysis are clearly and precisely documented and are readily available to any researcher for purposes of replication.

Consent for publication: All authors have reviewed the final version of the manuscript and approve it for publications.

Ethics approval and consent to participate: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (ATRSS-USTHB-ALGERIA) and with the Helsinki Declaration of 1975, as revised in 2008. All the patients signed the consent form for allowing their information to be used for research.

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