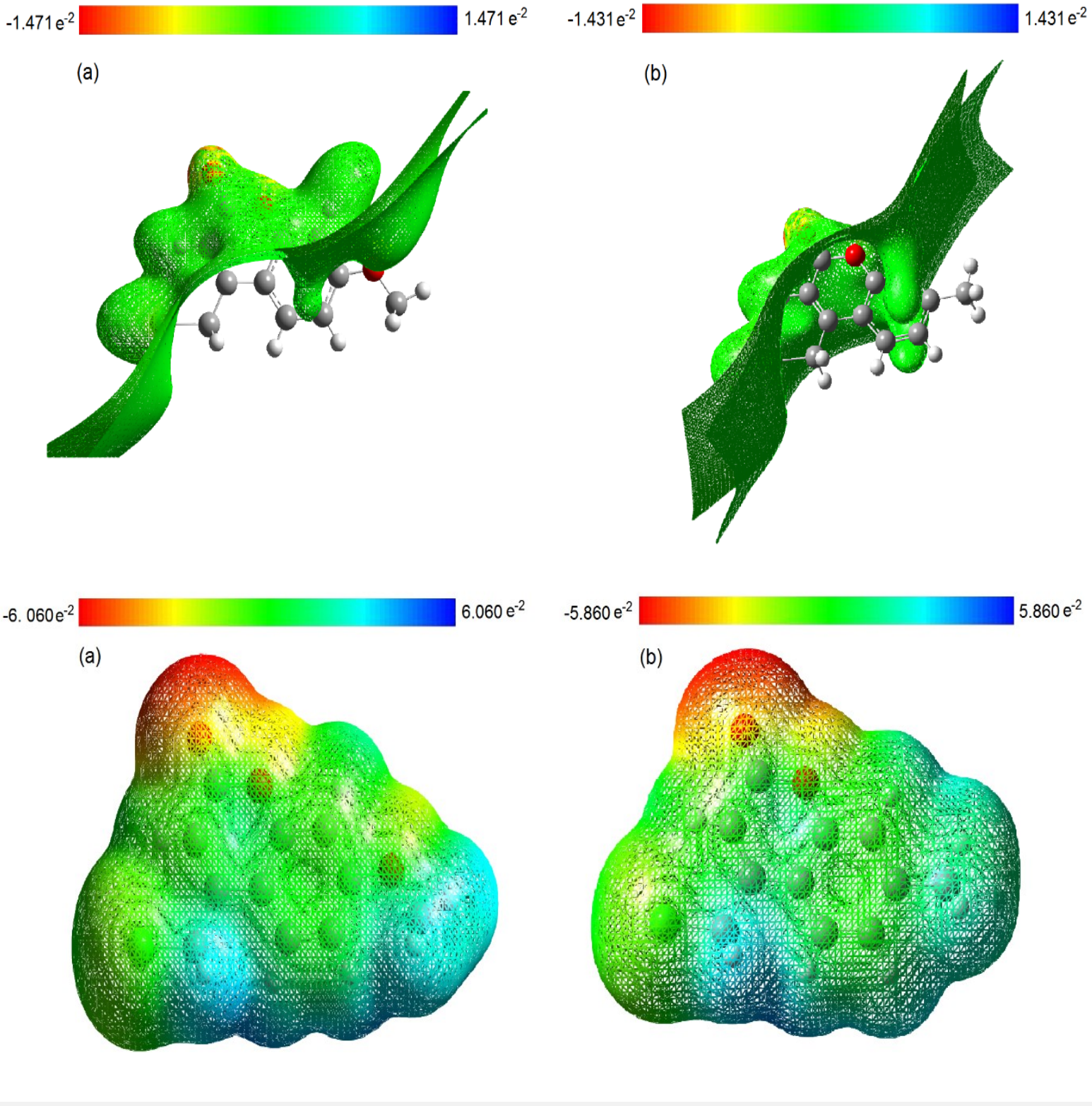
MSD
MEDICAL SCIENCE & DISCOVERY
ISSN: 2148-6832
Lycia Press LONDON UK



International Journal of
Medical Science and Discovery
Open Access Scientific Journal
August 2016, Vol.3, No.8
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ISSN: 2148-6832 (Print) E-ISSN: 2148-6832 (Online)
Category: Multi Disciplinary Health Science Journal
Abbreviated key title: Med. Sci. Discov.
Frequency: Monthly
Review System: Double Blind Peer Review
Circulation: Globally, Online, Printed
Article Processing Charge (APC): US$ 100
Licensing: CC-BY-NC 4.0 International License Environmental
Editor-in-Chief: Assoc. Prof. Dr. Zafer AKAN
Established: 30.04.2014
Address: CBU, Faculty of Medicine Dept. of Biophysics, Manisa, TURKEY
Web address: www.medscidiscovery.com; http://dergipark.ulakbim.gov.tr/msd
E-mail : editor [at] medscidiscovery.com
Phone : +90 236 233 1920 / 213

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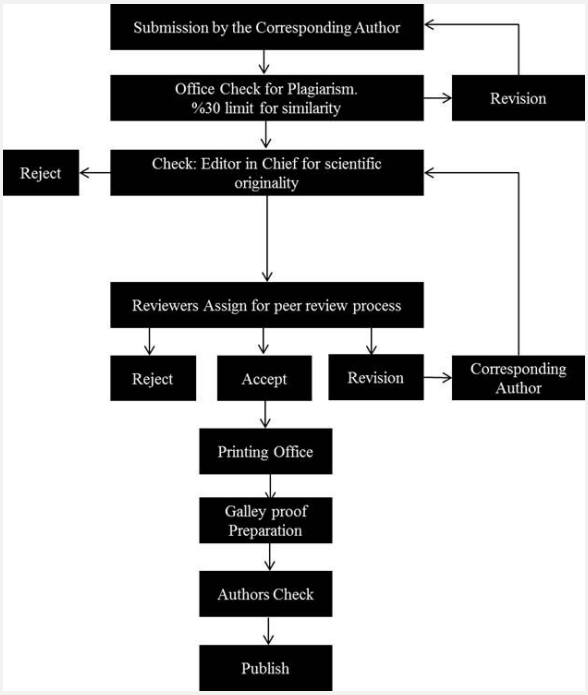

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Medical Science and Discovery, August 2016, Vol.3, No.8

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Case Reports

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ISSN: 2148-6832

MSD Medical Science and Discovery
2016; 3(8):296-300

Original Article Doi: 10.17546/msd.72369

Hepatitis a seropositivity and characteristics among healthcare workers in a training and research hospital in Istanbul

Ahmet Melih Sahin[1*], Ayse Tekin[2], Cem Basmaci[3], Nuray Uzun Kes[4], Emine Sonmez[5]

Abstract

Objective: In this study, we investigated the relationship between the socioeconomic status, living conditions, life span, working life timeand the seropositivity of HEPATITIS A Virus (HAV) infection among our hospital staff members.

Material and Methods: Anti-HAV IgG testing of randomly selected 167 healthcare workers were examined in 2012-2013. All participants answered on a questionnaire consisting questions on transmission routes and socioeconomic status.

Results: Overall HAV seropositivity was found to be %43.1 among healthcare workers with a mean age of 33.4for subjects with positive results and 27.4 years with negative results. Observed risk factors for seropositivity were the life span, professional working life time, life time in Istanbul, history of living in rural areas and frequent toilet usage outside of the house ($p < 0.05$). The factors that are inversely associated with seropositivity were educational level of parents, being born in Aegean-Mediterranean region, bottled water share in drinking water consumption and being a physician ($p < 0.05$).

Conclusion: In conclusion, HAV infections contniue to be a serious problem.Vaccination must be considered for seronegative healthcare workers and the public.

Key words: Hepatitis A Virus, Healthcare Workers, Risk Factors, Prevalence Seroepidemiologic Studies, Turkey

Introduction

Hepatitis A Virus (HAV) is an acute viral hepatitis factor commonly seen around the world and in Turkey. Our country falls within the moderate endemic group in terms of HAV epidemiology. 37% of the world's population still do not have connect to adequate sanitation and 11% is without access to any source of clean drinking water (1). Therefore, infectious diseases transmitted by faecal-oral route continue to constitute a problem (2).

In our country, seroprevalence of HAV increases with the school-age and, although reported differently in various studies, reaches the rates above 90% during adulthood (3, 4). However, recent studies showed that a significant decrease is started to be observed in this rate (5,6,7,8).

In this study, we examine the connection between the socioeconomic status, working and living conditions and the seropositivity of HAV infection among healthcare workers working at Şişli Hamidiye Etfal Training and Research Hospital.

Material and Methods

In this study, Anti-HAV IgG results of 167 healthcare workers worked at Şişli Hamidiye Etfal Training and Research Hospital in 2012-2013 were examined. Anti-HAV IgG was studied in serum samples with

ELISA method using DiaSorin, Saluggia, Italy kit and LiaiSon Immunoassay instrument. A questionnaire was applied to 167 participants, which contains questions on transmission routes and socioeconomic status.

Statistical method: Mean and standard deviation values were used in the explanatory statistics of data. Kolmogorov-Smirnov test was used for distribution of variables, Mann-Whitney U test was used for analysis of quantity of data, and Chi-square test and Fisher's

Received 25-04-2016 **Accepted** 26-05-2016 **Available Online** 15-08-2016
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exact test were used for analysis of qualitative data. SPSS 22.0 program was used in the analyses.

Results

Demographics of healthcare workers participated in study such as age, gender and place of birth and residence are provided in Table 1.

Anti-HAV IgG result was determined to be negative for 95 participants and positive for 72 participants. Mean age was 27.4 years for healthcare workers with negative Anti-HAV IgG result and 33.4 years for healthcare workers with positive

Anti-HAV IgG result. Age of the personal of Anti-HAV IgG positive group was determined to be higher than the individuals in Anti HAV IgG negative group ($p < 0.05$) (Table 1).

No important distinction was saw in gender distribution between the healthcare workers with negative and positive Anti-HAV IgG result ($p < 0.05$) (Table 1).

Anti-HAV IgG positivity rate was lower in individuals born in Aegean-Mediterranean region as compared to individuals born in the other regions ($p < 0.05$) (Table 1).

Anti-HAV IgG positivity was higher in individuals who lived in a village at some point in their lives when compared to individuals who never lived in a village ($p < 0.05$) (Table 1).

Period of time spent in Istanbul was longer in Anti-HAV IgG positive group compared to Anti HAV IgG negative group ($p < 0.05$) (Table 1).

Among the healthcare workers, Anti-HAV IgG positivity was lower for physicians when compared to other occupational groups ($p < 0.05$) (Table 2).

Professional time was detected to be longer in Anti-HAV IgG positive group in comparison to Anti HAV IgG negative group ($p < 0.05$) (Table 2).

Table 1: Some demographic characteristics of healthcare workers participated in study

		Hepatitis A				
		Anti-Hav IgG(-)		Anti-Hav IgG(+)		p
Age		27.4 ± 4.2		33.4 ± 6.9		***0.000***
		n	%	n	%	
Gender	Female	67	59.8	45	40.2	0.193
	Male	26	49.1	27	50.9	
Place of Birth	Aegean-Mediterranean	25	73.5	9	26.5	***0.028***
	Central Anatolia	10	41.7	14	58.3	0.164
	Southeastern Anatolia - Eastern Anatolia - Eastern Black Sea	24	52.2	22	47.8	0.448
	Marmara - Western Black Sea	36	59.0	25	41.0	0.673
	Bulgaria	0	0.0	2	100.0	
Living Area	Always lived in a city	66	61.1	42	38.9	0.136
	Lived in a town for some time or permanently	24	66.7	12	33.3	0.181
	Lived in a village for some time or permanently	5	21.7	18	78.3	***0.000***
How long do you live in Istanbul (years)?		10.2 ± 9.6		17.2 ± 12.1		***0.000***
Mann-Whitney U test / Chi-square test						

Table 2: Occupational distribution and professional time of healthcare workers

	Hepatitis A						p
	Anti-Hav IgG(-)			Anti-Hav IgG(+)			
Professional Time	4.1	±	3.9	9.0	±	7.1	***0.000***
Profession	n		%	n		%	
Physician	58		65.2	31		34.8	***0.021***
Nurse - Lab. Technician	28		53.8	24		46.2	0.594
Allied Health Personnel	0		0.0	16		100.0	***0.000***
Secretary	9		90.0	1		10.0	***0.029***

Table 3: Nutritional habits of healthcare workers

		Hepatitis A				p
		Anti-Hav IgG(-)		Anti-Hav IgG(+)		
		n	%	n	%	
Water Consumption	Bottled Water	62	68.1	29	31.9	***0.001***
	Municipal Water-Other	33	43.4	43	56.6	
Habit of Eating Out	Less than once a week	14	32.6	29	67.4	***0.001***
	Once a week	21	67.7	10	32.3	
	2-3 times a week	34	58.6	24	41.4	
	4 or more times a week	26	74.3	9	25.7	
Location of Toilet at the Place You Lived in the Past	Inside the house	93	60.4	61	39.6	***0.002***
	Outside the house	2	15.4	11	84.6	

Table 4: Income distribution of healthcare workers

		Hepatitis A				p
		Anti-Hav IgG(-)		Anti-Hav IgG(+)		
		n	%	n	%	
Monthly Income	<1000	2	33.3	4	66.7	0.504
	1000-2500	34	53.1	30	46.9	
	2500-5000	50	61.0	32	39.0	
	>5000	9	69.2	4	30.8	
How many people live in your household?	3	19	50.0	19	50.0	***0.022***
	4-5	66	64.7	36	35.3	
	>6	10	37.0	17	63.0	

Table 5: Educational level of parents of healthcare workers

		Hepatitis A				p
		Anti-Hav IgG(-)		Anti-Hav IgG(+)		
		N	%	n	%	
Educational Status of Mother	None	8	30.8	18	69.2	***0.000***
	Primary school	31	47.7	34	52.3	
	Secondary school	14	58.3	10	41.7	
	High school	21	80.8	5	19.2	
	University	21	80.8	5	19.2	
Educational Status of Father	None	1	25.0	3	75.0	***0.000***
	Primary school	17	32.7	35	67.3	
	Secondary school	9	69.2	4	30.8	
	High school	25	75.8	8	24.2	
	University	43	66.2	22	33.8	

Healthcare workers were asked questions addressing the infrastructure services such as their drinking water source, habit of eating out, and toilet use and location. Anti-HAV IgG positivity rate was lower in individuals who mainly drink bottled water as compared to individuals who use other sources of water ($p < 0.05$) (Table 3). Anti-HAV IgG positivity rate was significantly high in individuals who used a toilet outside the house at some point in their life ($p < 0.05$) (Table 3).

No difference was detected when healthcare workers were compared for their monthly income and number of people per household ($p < 0.05$) (Table 4).

Anti-HAV IgG positivity rate was detected to decrease as the educational level of the parents of healthcare workers increased ($p < 0.05$) (Table 5).

Discussion

Although 1,400,000 new hepatitis A virus infections consist globally every year, the prevalence of Hepatitis A tends to decrease except for the underdeveloped and developing countries (2). This was associated with improvements in adherence to hygiene rules, decrease in infrastructure problems, and increases in socio-economic development and educational level. Although our country belongs to the moderate endemic group, various seropositivities were detected in the studies conducted in different regions (5, 6, 7). Various studies in healthcare workers and community in our country show that the anti-HAV IgG positivity increases with the age, reaching the rates above 90% in adult population (4,5,6,7).

In a study evaluating the prevalence of anti-HAV IgG positivity in healthcare workers and students, anti-HAV IgG was detected to be positive in 92.2% of the nurses, for whom the mean age was higher, and 57.5% of the nursing students (9).

In our study, mean age of healthcare workers with positive anti-HAV IgG result was found to be markedly higher than the group with negative anti-HAV IgG result ($p< 0.05$) (Table 1).

HAV seropositivity is reported within the range of 7.8% to 88% in different regions of our country (11). In our study, seronegativity rates were higher in healthcare workers born in Aegean and Mediterranean regions ($p<0.05$) (Table 1). This was attributed to more developed socio-economic status of these regions.In their study, Ozkınay et al. (12) found significantly higher rates for anti-HAV IgG positivity in individuals living in villages. In another study conducted in Iran, prevalence was determined to be markedly higher in the region with infrastructure problems (13). In our study, anti-HAV IgG positivity rate was found to be higher in individuals who lived in a village at some point in their lives and in individuals who lived in Istanbul for a longer timeof time ($p< 0.05$). This was considered as an indication that the infrastructure and sanitation problems are not only experienced in villages but also in mega-villages, where population grows rapidly, such as Istanbul.Anti-HAV IgG positivity rate was found to be higher in healthcare workers with a longer professional time ($p< 0.05$) (Table 2).

As with the other infectious diseases, this may indicate that the occupational exposure increases with the increased professional time. It is reported that the educational status of parents, especially the mother, is closely associated with Anti-HAV IgG positivity rate and the prevalence decreases as the educational level increases (11,12).

A study conducted in USA showed that the seropositivity was decreased as the years of school attendance of parents increased (14).

In a study performed by Erdogan et al. (15), it was observed that the HAV seropositivity was decreased as the educational level of mother increased.

Our study determined that the HAV seronegativity was increased with the increased educational level ($p < 0.05$) (Table 5). This can be explained by the fact that the better life conditions can be ensured as the educational level increases because it leads to improvements in awareness of diseases transmitted by faecal-oral route, personal hygiene, water and food hygiene, and socio-economic status. Study of Erdogan et al. (15) detected a markedly higher prevalence in low- and low-moderate-income individuals (59.4% and 30.8%, respectively).

In the study of Aldeniz et al. (4), a significant difference was determined between the groups with good and poor economic conditions (80.2% and 94%). In a study performed in Spain, a higher seropositivity was detected in people, who were born outside Spain and who were from a lower social class (16).

Our study found no important relationship between Anti-HAV IgG positivity and monthly income ($p > 0.05$ (Table 4).Seronegativity was found to be significantly higher in individuals who drink prepared/bottled water ($p <0.05$) (Table 3).

Also in other studies, seronegativity was found to be higher in groups composed of individuals drinking clean and safe water (14, 15, 17).

Conclusion

In conclusion, the incidence of hepatitis A infections can be decreased by resolving the infrastructure problems, increasing the educational level and improving the hygiene conditions.

Improvements in these conditions delay the onset of disease to a later age during adulthood in our country. Vaccination of susceptible adults can be recommended when considering the fact that the course of disease become more serious in adulthood. This is even more important for healthcare workers with seronegative results and the disease and its complications can be decreased with the vaccination

programs for this population. We believe that the vaccination programs will ensure immunisation of both the healthcare workers and the public, and contribute to eradication of disease over time and will also decrease the related complications, mortality and cost.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

Aknowledgement: None

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http://www.medscidiscovery.com
OPEN ACCESS JOURNAL

ISSN: 2148-6832

MSD Medical Science and Discovery
2016; 3(8):301-4

Original Article Doi: 10.17546/msd.57676

Comparison of the effects of two different dose algorithms in cardiac dose parameters for hodgkin lymphoma patients receiving mediastinal radiotheraphy

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Abstract

Objective: This study aimed to compare pencil beam (PB) and convolution superposition (CS) dose calculation algorithms with respect to cardiac dose-volume parameters V5, V25, V30 and MHD (median heart dose) in Hodgkin lymphoma (HL) patients who received mediastinal radiotherapy (RT).

Material and Methods: Ten eligible cases with the diagnosis of HL who completed mediastinal RT at Dokuz Eylül University Department of Radiation Oncology before 01.01.2011 formed the study population. Related 3D conformal RT treatment plans were obtained from the Treatment Planning System (TPS) (Nucletron Oncentra Master Plan Version 3.3 SP3 program). Calculations were done for 6 and 18 MV-X beam energy, respectively by using PB and CS algorithms in the TPS. Two algorithms were compared in terms of cardiac dose-volume parameters (V5, V25, V30 and MHD).

Results: Mean relative difference for both V25 and V30 was found to be significantly higher in favor of PB algorithm in both 6 MV-X and 18 MV-X photon energy. Mean relative differences were 1.75% (p=0.012) and 6.76% (p=0.028) for the V25 and V30 parameters, respectively in 6 MV-X and 3.25% (p=0.021) and 13.95% (p=0.007) for the V25 and V30 parameters, respectively in 18 MV-X energy.

Conclusion: When PB algorithm is used in RT treatment planning of HL patients for the mediastinal region where tissue inhomogeneity is relatively high, heart V25 and V30 parameters were shown to result in higher values compared to CS algorithm in our study. It is more appropriate to prefer CS algorithm instead of PB algorithm since it increases accuracy of calculations in the treatment planning of mediastinal RT.

Key words: Convolution / superposition, pencil beam, Hodgkin lymphoma, cardiac dose-volume parameters

Introduction

Radiotherapy (RT), which plays an important role in the traetment of Hodgkin's lymphoma (HL), has complications related with technique, dose and irradiated volume (1).

In HL, bilateral hilar lymhatic regions should always be included in mediastinal RT volume according to the recommendations related to "Involved Field Radiotherapy" (IFRT). Therefore, bilateral lung tissue constitute inhomogeneity together with trachea, main bronchi and mediastinal soft tissue in mediastinal RT. Heart is exposed to a significant portion of the targeted dose in various extent since it is located partially within the RT field.

Thus, mediastinal RT volume in patients with HL is considered to be an appropriate region for the comparison of pencil beam (PB) and convolution/superposition (CS) algorithms. Despite the development of quicker and more sensitive novel diagnostic techniques, their complexity and high cost have limited their use in many poor-resource countries.

Due to the rapidly growing TB problem in these countries, there is an urgent need to assess promising alternative methodologies in settings with high disease prevalence (6).

Received 15-06-2016 **Accepted** 20-06-2016 **Available Online** 15-08-2016
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In this study, we aimed to examine the relationships between EZN, culture and PCR and to investigate whether an algorithm has been used in the administration of these methods.

Material and Methods

Ten eligible cases with the diagnosis of HL who completed mediastinal RT at Dokuz Eylül University Department of Radiation Oncology before 01.01.2011 formed the study population. Related 3D conformal RT treatment plans were obtained from the Treatment Planning System (TPS) (Nucletron Oncentra Master Plan Version 3.3 SP3 program). Selection criteria were; being diagnosed as HL, at least 1/3 of the heart being included in the mediastinal RT field (mantle, modified mantle, only mediastinum + bilateral hilar regions), 3-dimensional conformal treatment plan being performed in Nucletron Oncentra computed TPS, being treated to a dose of at least 30 Gy. PTV and OAR (Organ at Risk) delineation were performed according to our institution's protocols on the Oncentra MasterPlan image registration module, with CT slice intervals of 5 mm acquired under normal respiration conditions in the CT-simulator.

Calculations were redone for 6 and 18 MV-X beam energy, respectively by using PB and CS algorithms in the TPS. For each patient's treatment plan, all plan elements (beam angles, beam energies, beam weights, etc.) were the same in both calculations using two different algorithms. The same reference isodose was chosen for each treatment plan formed with the same beam energy using PB and CS algorithm. Under these conditions, V5, V25, V30 and median heart dose (MHD)) values were obtained from DVHs.

Two algorithms were compared in terms of cardiac dose-volume parameters (V5, V25, V30 and median heart dose (MHD)). Statistical analysis was performed using SPSS 15.0 program. Since the number of patients was below 30, a non-parametric test had to be used. Also, the Wilcoxon signed rank test was preferred due to the comparison of two related data. For statistical significance, the p value was accepted to be smaller than 0.05.

Results

V5, V25, V30 and MHD parameters were documented at the end of calculations done for different algorithms on the plans of the cases.The results related to dose-volume parameters of cases are given for 6 MV-X and 18 MV-X in Table 1 and Table 2, respectively.According to the data given in Table 1 and 2, mean V25, V30 and MHD values are higher in PB algorithm, while mean V5 parameter is higher in CS algorithm for both 6 MV-X and 18 MV-X energy.Statistical analysis results of the comparison of PB and CS algorithm is demonstrated in Table 3. As it can be seen from the results related to 6 MV-X energy in Table 3, only V25 and V30 showed statistically significantly higher values in PB algorithm compared to CS algorithm (p=0.012 and p=0.028, respectively). As for 18 MV-X energy, again only V25 and V30 showed statistically significantly higher values in PB algorithm compared to CS algorithm (p=0.021 and p=0.007, respectively).

Discussion

Since it affects the long term survival, the importance of reducing the late cardiac side effects of RT is clear. In RT treatment planning, it becomes more important to calculate cardiac dose-volume parameters accurately for the prediction of cardiac toxicity. RT parameters that define the risk of a cardiac event are dose and irradiated volume (1, 2)In order to minimize cardiac mortality, Dabaja et al. used V5 and V30 parameters in their RT technique developed to reduce heart and breast doses in mediastinal RT of HL patients (3). During implementation of RT in patients with mediastinal HL, Ghalibafian et al. took into account V30 as well as MHD in intensity modulated RT (IMRT) applied for the protection of heart and coronary arteries (4). Similarly, Girinsky et al. used V30 and MHD parameters in a study comparing IMRT, 3-D conformal RT and conventional RT in HL patients with mediastinal involvement (5). Ung et al. used V25 parameter for the heart volume remaining within the RT field during chest wall irradiation in breast cancer patients who had mastectomy (6). There is not any study performed in HL patients treated with mediastinal RT which compares PB and CS algorithms in terms of cardiac dose-volume parameters. In our study, PB and CS algorithms were compared using heart V5, V25, V30 and MHD parameters in this group of patients.

Scholz et al. showed that the mean PTV dose was calculated as 8% and 1.5% higher with PB algorithm in the lung and head-neck tissue in which inhomogeneity is evident (7).In the study of Vanderstraeten et.al., the mean relative difference between the PB and CS algorithms using 6 MV-X energy was found as -2.4% (p=0.030) for lung V30 parameter, -1.0% (p=0.008) for heart D33 parameter and -2.04% (p=0.105) for heart Dmax parameter, values being higher with PB algorithm compared to CS algorithm (8). In the same study, the mean relative difference between the PB and CS algorithms using 18 MV-X photon energy was found as -0.06 % (p=0.999) for lung V30 parameter, -0.77 % (p=0.006) for heart D33 parameter, and -1.17 % (p=0.348) for heart Dmax parameter values being higher with PB algorithm compared to CS algorithm (8).

Table 1. Minimum, maximum and mean ± standard error values of V5, V25, V30 and HD parameters in the formed plans by using PB and CS algorithms for 6 MV-X photon energy

6 MV-X								
	V_5 (%)		V_{25} (%)		V_{30} (%)		MHD (cGy)	
	PB	CS	PB	CS	PB	CS	PB	CS
Mean	83.90	84.48	57.10	56.10	36.37	33.91	2443.70	2387.70
Std. E.	3,78	3,89	6,55	6,61	9,67	9,94	215.75	194.14
Min	65.58	64.94	38.38	37.21	12,43	12,29	1327.00	1379.00
Max.	100	100	100.00	100.00	98.93	98.93	3500.00	3181.00

Mean, Std. E: standard error, Min: minimum, Max: maximum, V5: percent (%) value of heart volume receiving at least 5 Gy radiation dose, V25: percent (%) value of heart volume receiving at least 25 Gy radiation dose, V30: percent (%) value of heart volume receiving at least 30 Gy radiation dose, MHD: Median heart dose, PB: pencil beam, CS: convolution/superposition

Table 2. Minimum, maximum and mean ± standard error values of V5, V25, V30 and MHD parameters in the formed plans by using PB and CS algorithms for 18 MV-X photon energy

18 MV-X								
	V_5 (%)		V_{25} (%)		V_{30} (%)		MHD (cGy)	
	PB	CS	PB	CS	PB	CS	PB	CS
Mean	84.22	84.67	58.04	56.15	38.70	33.30	2463.70	2444.60
Std. E.	4,03	3,79	6,98	6,61	9,41	9,73	213.63	203.81
Min.	65.58	65.58	38.43	35.86	11,83	7,10	1380.00	1443.00
Max.	100	100	100.00	100.00	93.40	94.83	3578.00	3490.00

Mean, Std. E: standard error, Min: minimum, Max: maximum, V5: percent (%) value of heart volume receiving at least 5 Gy radiation dose, V25: percent (%) value of heart volume receiving at least 25 Gy radiation dose, V30: percent (%) value of heart volume receiving at least 30 Gy radiation dose, MHD: Median heart dose, PB: pencil beam, convolution/superposition

Table 3. Comparison results of PB and CS algorithms in terms of cardiac dose-volume parameters by using Wilcoxon signed rank test ($p<0.05$ shows statistically significant differences).

	6 MV-X				18 MV-X			
	Mean Values		Mean Relative Difference	p	Mean Values		Mean Relative Difference	P
	PB	CS			PB	CS		
V_5 (%)	83,90	84,48	0.01%	0.173	84,22	84,67	0.01%	0.213
V_{25} (%)	57.10	56.10	- 1.75%	**0.012**	58.04	56.15	- 3.25%	**0.021**
V_{30} (%)	36.37	33.91	- 6.76%	**0.028**	38.70	33.30	- 13.95%	**0.007**
MHD (cGy)	2443.7	2387.0	- 2.32%	0.169	2463.7	2444.6	- 0.01%	0.241

V5: percent (%) value of heart volume receiving at least 5 Gy radiation dose, V25: percent (%) value of heart volume receiving at least 25 Gy radiation dose, V30: percent (%) value of heart volume receiving at least 30 Gy radiation dose, MHD: Median heart dose, PB: pencil beam, CS: convolution/superposition, Mean Relative Difference: CS value – PB value / PB value x 100

Also in our study, significant differences were observed in favor of PB for heart V25 and V30 for 6 MV-X and 18 MV-X energy. Although the cardiac parameters used in our study is different than in Vanderstraeten et.al.'s study, they are in accordance with the results of that study.

The mean relative difference between PB and CS algorithms in terms of heart V25 and V30 was higher for 18 MV-X than the difference for 6 MV-X energy. This can be explained as follows: Since CS algorithm takes into account the effect of secondary electron scattering on dose distribution depending on the tissue density, it is able to calculate the dose distribution on the mediastinum-lung tissue interface more accurately compared to PB algorithm. As energy level increases, the effect of electron scattering becomes more evident

Since CS algorithm is close to Monte Carlo algorithm with regard to sensitivity in calculation and requires shoter calculation time than Monte Carlo algorithm, it can be said that CS algorithm has the balance of speed and accuracy**.**

Conclusion

In our study, cardiac dose-volume parameters (V25 and V30) were found to have significantly higher values in favor of PB algorithm. It was observed that these differences were more apparent for 18 MV-X than for 6 MV-X energy. These results are similar to the results obtained by Vanderstraeten et. al. who used different cardiac dose-volume parameters from our study.

The sensitivity of CS algorithm is close to Monte Carlo algorithm and calculation time is shorter. Moreover, in our study, the difference detected between PB and CS algorithms is statistically significant. Therefore, it is more suitable to use CS algorithm instead of PB algorithm in order to increase the accuracy of calculated dose distribution in HL patients who receive mediastinal RT, similarly to head-neck and lung cancer patients who have particularly evident tissue inhomogeneity within their RT fields.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

Aknowledgement: None

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http://www.medscidiscovery.com
OPEN ACCESS JOURNAL

ISSN: 2148-6832

MSD Medical Science and Discovery
2016; 3(8):305-11

Original Article Doi: 10.17546/msd.90383

The Clinical Significance of the Neutrophil-to-Lymphocyte Ratio in Patients with Guillain-Barré Syndrome Independent of Infection

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Abstract

Objective: In the present study, we aimed to determine the predictive value of neutrophil-to-lymphocyte ratio (NLR) in the diagnosis of Guillain-Barré Syndrome (GBS).

Material and Methods: This retrospective study enrolled 94 GBS patients and a control group of 101 healthy subjects.

Results: GBS patients had significantly higher NLR, C- Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) values at presentation than the healthy control group ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively). Patients unresponsive to IVIg therapy had significantly higher NLR values at the time of admission in comparison to responsive patients ($p=0.001$). NLR was significantly and positively correlated with the disease severity, CRP and ESR. A receiver operating characteristic (ROC) analysis of the ability of NLR to predict GBS showed a cutoff value of 3.5 (sensitivity 62.8%, specificity 90.1%). The cutoff value was 11 for CRP (sensitivity 52.7%, specificity 86%) and 12.3 for ESR (sensitivity 51.3%, specificity 82%). Exclusion of patients with signs of infection at presentation gave a NLR value of 3.2, which had a sensitivity of 61.6% and a specificity of 89.8% for predicting GBS.

Conclusion: Whereas ESR and CRP lost their significance in predicting GBS. Unlike ESR and CRP, NLR might be a promising marker in GBS regardless of infection.

Keywords: Guillain-Barré Syndrome, neutrophil-to-lymphocyte ratio, C-reactive protein, erythrocyte sedimentation rate

Introduction

Guillain-Barre Syndrome (GBS) is a progressive immune-related polyradiculoneuropathy that is the most common cause of acute and progressive generalized paralysis (1). There is still little knowledge on the biochemical and immunological markers that can be used to support the diagnosis of GBS. Most patients (60% to 70%) have a history of surgical intervention, vaccination or infections, such as an upper respiratory or gastrointestinal infection, that often predate the onset of neurological symptoms by 4 weeks (2).

Several clinical subtypes of GBS have been identified, such as including acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), Miller Fisher Syndrome (MFS), acute pandysautonomia and acute sensory neuropathy (3).

Both cell-mediated immunity and humoral mechanisms are involved in the pathogenesis (4, 5).

The effectiveness of plasmapheresis and intravenous immunoglobulin (IVIg) was demonstrated in randomized trials (6, 7).Recently, the blood neutrophil-to-lymphocyte ratio (NLR) has been studied as a biomarker for systemic inflammation in a number of neurological disorders (8-10) and was found to be associated with a poor prognosis in certain diseases (11). Considering the integral role of inflammation in the development of GBS, we focused on three systemic inflammation markers in affected patients, namely the neutrophil-to-lymphocyte ratio, C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR). To our best knowledge, NLR has not been previously studied in GBS patients.

Received 17-06-2016 **Accepted** 21-06-2016 **Available Online** 15-08-2016
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Thus, in the current study, we aimed to determine the predictive value of NLR, CRP and ESR in the diagnosis of GBS during the acute phase and to investigate the correlation of NLR with the severity and subtype of the disease, as well as the role of the response to IVIg treatment in GBS patients.

Material and Methods

Study population:

This study is a hospital-based retrospective investigation. Study approval was obtained from the Ethics Committee of Gaziantep University Faculty of Medicine, Turkey. Electronic medical records of 124 patients who were diagnosed with GBS (according to Asbury and Cornblath's diagnostic criteria)(12). 19 at an inpatient clinic of neurology (Department of Neurology, Gaziantep University Sahinbey Research Hospital, Gaziantep/Turkey) between January 2008 and January 2015 were reviewed retrospectively. Patients who were subsequently diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP) during follow-up visits after being hospitalized with GBS were excluded. Additionally, patients with a history of alcoholism, diabetes mellitus or exposure to toxic substances, metals or drugs that could cause acute neuropathy and patients with inadequate data were excluded.

Thus, 94 eligible patients not meeting these exclusion criteria were enrolled. The data reviewed for study patients included age, gender, history of antecedent infections, signs of infection at the time of admission (based on clinical and blood parameters), electrophysiological findings, clinical features, information related to treatment, and duration of hospitalization. All GBS patients were classified electro physiologically as AIDP, AMAN or AMSAN using motor nerve conduction criteria (13). The GBS disability score (Hughes grade scale) was used to evaluate the disease severity during hospitalization and the first outpatient appointment (ranging from 3 weeks to 1 month after discharge)(14). Venous blood values at the time of presentation (within a mean period of 5.4±2.7 days after the onset of symptoms (min: 1, max: 15) and those obtained at the first occasion following administration of IVIG (0.4 g/kg/day continuously for 5 days) treatment (min: 2 and max: 10 days) for any reason were recorded for all patients. Sixteen (17%) patients treated with plasmapheresis after IVIg treatment because of a worsened neurological examination, despite receiving IVIg treatment.

A second set of blood samples were taken before the plasmapheresis. Post-treatment hemogram values were available for all 94 patients, but only 22 patients had both CRP and ESR values available; thus, only post-treatment NLR values were recorded. Healthy controls (n=101) matched for age and gender who were admitted to our hospital for routine check-up were randomly chosen from the hospital database if they did not have any symptoms of peripheral neuropathy, clinical signs or laboratory findings suggestive of an infection or a history of chronic illnesses, malignancy or rheumatic disorders.

ESR was measured using the traditional Westergren method. CRP levels were quantified using a nephelometric assay on a Dade Behring Nephelometer BN II device (Siemens Healthcare GmbH, Erlangen, Germany). CBC analysis was performed with a Beckman Coulter (High Wycombe, UK) Gen-S automated analyser within 2 hours of blood sampling. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count in a complete blood count taken before and after IVIg treatment.

Statistical Method:

Student's t-test was used to compare normally distributed numerical variables in two independent groups, and the Mann–Whitney U test was used for non-normally distributed numerical variables. An ANOVA and Fisher's least significant difference (LSD) multi-comparison test were employed to compare normally distributed variables in more than two groups, whereas the Kruskal–Wallis test was used for non-normally distributed variables. Pearson's coefficient of correlation was used to test correlations between numerical variables, and a chi-square test was used for the analysis of correlations between categorical variables.

Receiver operating characteristic (ROC) curves were used to determine the cutoff values for NLR. For descriptive statistics, data are presented as the mean ± standard deviation for numerical variables and the number and percentage for categorical variables. SPSS for Windows version 22.0 software package was used for statistical analyses, and a p value less than 0.05 was considered statistically significant.

Results:

The study enrolled a total of 94 GBS patients, including 32 females and 62 males with a mean age of 48.7±20.6 years (18-86). The control group consisted of a total of 101 healthy individuals (47 females, 54 males) with a mean age of 50.63±19.025 years (18-80). The demographic data, clinical characteristics and blood biochemistry values of the study population are summarized in Table I.

Electrophysiological classification of the GBS patients revealed the following subtypes: AIDP (n = 64), AMAN (n = 16) and AMSAN (n = 14). The mean duration from the onset of symptoms to the confirmed diagnosis of GBS was 5.4±2.7 days (1-15). The mean Hughes score of patients at the initial examination was 3.53±0.49.

Table 1: Demographic Data, Clinical Characteristics, and Blood Biochemistry Values of the Study Population (mean ± SD)

Variable	Controls (n=101)	Patients (n=94)	p value
Age (year)	50.63±19.025	48.7±20.6	0.497
Gender **Female (n %)** **Male (n %)**	 47 (46.5) 54 (53.5)	 32(34) 62(66)	 0.076
BMI	26.53±2.19	26.231±2.35	0.062
NLR **At presentation** **After IVIg treatment**	 2.53±0.94	 5.43±3.98 2,61±0.69	0.001*∞ 0.699° 0.001*≠
WBC (10^9/l) **At presentation** **After IVIg treatment**	 8.78±1.3	 9.42±2.32 8.99±1.9	0.089∞ 0.078≠ 0.081°
Hgb (/µ) **At presentation** **After IVIg treatment**	 13.67±1.32 -	 13.12±1.12 13.06±1.06	 0.127∞ 0.106° 0.118≠
CRP (mg/dl), median (min-max) **At presentation**	 3.7±1.2 (0.05-6.5)	 16.3±14.2 (2.2-86)	 0.001*∞
ESR (mm/h), median (min-max) **At presentation**	 6.4 (1-12)	 16.13±14.3 (4-110)	 0.001*
Hughes score **At presentation** **At 1 month** **Reduction**	 - -	 3.53±0.49 2.09±0.72 1.44	 0.001*≠

*p<0.005 ∞ comparison between GBS patients and controls before treatment
≠ pre-treatment/post-treatment comparison in GBS patients
° pre-treatment/post-treatment comparison between GBS patients and controls

Table 2. Associations between clinical characteristics and pre-treatment/post-treatment NLR values

Variable	n (%)	NLR[1]	NLR[2]	p value
Response to IVIG treatment **Yes** **No** **p value**	 78 (83) 16 (17)	 4,67±3,57 9,10±3,89 0.001*	 2,48±1,58 3,23±2,11 0.171	 0.001* 0.001*
Clinical subtypes **AIDP** **AMAN** **AMSAN** **P value**	 64 (68) 16(17) 14 (15)	 5,41±3.09 5.82±3.09 7,04±3.98 0.252	 3.61±1.41 3.12±1.07 4.46±2.01 0.345	 0.001* 0.001* 0.001*
Signs of infection at presentation **Yes** **No** **P value**	 11(11.7) 83(88.3)	 9.54±5.98 5.15±3.594 0.001*	 4.12±3.13 3.98±2.89 0.135	 0.001* 0.003*
History of infection **Yes** **No** **P value**	 48 46	 6.16±4.3 4.60± 3.8 0.009	 5.04±2.3 3.57±1.8 0.012	 0.360 0.302

1 values of GBS patients at admission at hospital, 2 values of GBS patients after IVIg treatment, * p<0.005

All 94 patients were given IVIg as the baseline therapy. Of these 94 patients, 78 (83%) benefited from this therapy and 16 (17%) continued their treatment with plasmapheresis therapy due to deterioration of their neurological findings, despite IVIg treatment. Six patients (6.4%) receiving both therapies died as a result of clinical deterioration.

Among these 6 patients, the cause of death was sepsis in 4 patients, pulmonary embolism in 1 patient, and 1 patient developed sudden cardiac arrest that was possibly associated with severe autonomic involvement. The mean duration of the hospital stay for all patients was 16.9± 5.4 days (12-90 days). Seventeen patients (18.08%) received antibiotherapy for treatment of intercurrent infections both at presentation and during hospitalization. The mean Hughes score of patients was 2.09±0.72 at the follow-up examination conducted within 3 weeks to 1 month after discharge. There was no significant difference between patient and control groups with respect to age, gender and BMI (Table I). The mean NLR value for patients at presentation (5.43±3.98) was significantly higher than that for the control group (2.53±0.94) (p=0.001), but the values for patients after IVIg treatment (2.61±0.69) were not significantly different from those for controls (p=0.699).

Significantly reduced NLR values were found after IVIg treatment among patients (p=0.001) (Table I).

The mean CRP value for patients at presentation (16.3±14.2 mg/dl) was significantly higher compared to that for the control group (3.7±1.2 mg/dl; p=0.001). Similar findings were also observed for ESR (Table I). When patients were divided into two subgroups based on the IVIg treatment response, the patients unresponsive to IVIg therapy showed significantly higher NLR values at presentation compared with the treatment-responsive patients (p=0.001) (Table II).

At presentation, the mean Hughes score was 3.48±0.38 for patients responding to IVIg and 3.69±0.72 for non-responsive patients, but the difference was not statistically significant (p=0.149). When we classified the patients according to the demyelinating form (AIDP) and axonal form (AMAN and AMSAN) subtypes, we observed the application HGS was higher in the axonal form (p=0.001). NLR values at presentation did not differ significantly between the disease subtypes (p=0.252). Eleven (11.7%) patients had signs of infection (both clinical and laboratory) at presentation, and a significant difference was found between the mean NLR values of infected patients (9.54±5.98) and non-infected patients (5.15±3.94) at presentation (p=0.001). CRP and ESR showed similar findings (Table III).

Based on the medical history, among the patients with clinical signs of infection at presentation, 31 patients (32.9%) had experienced an URTI and 17 (18.1%) patients had experienced diarrhoea within the last month. Patients with a history of infection had a mean NLR of 6.16±4.3, which did not differ significantly from the mean NLR of patients without such a history (4.60±3.80; p=0.009).

Analyses for the correlation between the disease severity and NLR revealed a significant positive correlation for patients between HGS at presentation and NLR values at presentation (r=0.383, p=0,000). A significant positive correlation was also found between the HGS at the follow-up visit within 3 weeks to 1 month after discharge and NLR at presentation (r=0.363 p=0,000). There was a mean improvement of 1.44 points in the HGS following treatment, and a significant negative correlation was observed between the magnitude of improvement in HGS and NLR values at presentation and post-treatment (r=-0.312 p= 0.002 and r=-0.288, p= 0.005, respectively). The application NLR was positively correlated and significantly associated with the length of the hospital stay (r=0.296; p=0.004). NLR at presentation was significantly associated and positively correlated with CRP and ESR at presentation (r=0.351, p=0.001 and r=0.338, p=0.001, respectively).

As determined by the ROC analysis, a NLR value of 3.5 had a 62.8% sensitivity and 90.1% specificity for predicting GBS (the area under curve (AUC), 0.772±0.035; p<0.001). A CRP value of 11 had a 52.7% sensitivity and an 86% specificity for predicting GBS (AUC=0.717±0.0374; p<0.001). An ESR value of 12.3 had a 51.3% sensitivity and an 82% specificity for predicting GBS (AUC=0.698±0.312; p=0,003) (Figure I).

Exclusion of 11 patients with signs of infection at presentation yielded a NLR value of 3.2, which was associated with a 61.6% sensitivity and an 89.8% specificity for predicting GBS (AUC= 0.752±0.031, p<0.001). In these patients, A CRP value of 7.5 had a 48.7% sensitivity and 63% specificity for predicting GBS (AUC=0.645±0.0305; p=0.105). An ESR value of 8.3 had a 46.3% sensitivity and 61% specificity for predicting GBS (AUC= 0.612±0.0317; p=0.137) (Figure II).

Discussion

Based on the results of this study, we found that NLR values were significantly higher in GBS patients than in healthy controls. A NLR value of 3.5 predicted the presence of GBS with a 62.8% sensitivity and 90.1% specificity. The cutoff value for the NLR for predicting GBS, regardless of infection, was 3.2 with a 61.6% sensitivity and an 89.8% specificity.

GBS is an acute inflammatory process that involves the peripheral nerves and nerve roots, and both humoral and cell-mediated immunity mechanisms play an integral role in its pathogenesis (5).

http://dx.doi.org/x10.17546msd.90383

Recently, NLR has been recognized as a simple and cost-effective peripheral biomarker that indicates the inflammatory status because it is believed to reflect the numerical balance between neutrophils and lymphocytes in the blood (9,10,15,16). CRP and ESR are elevated in the event of systemic inflammation, and combined use of ESR and CRP was considered to be more appropriate as inflammatory markers (17).

In the present study, GBS patients had significantly higher NLR, CRP and ESR values compared to healthy controls at presentation. These parameters are known to be influenced by infection (18). Therefore, when we removed the patients with clinical or laboratory signs of infection, the predictive significance of CRP and ESR disappeared, but an NLR value of 3.2 showed a 61.6% sensitivity and an 89.8% specificity for predicting GBS that remained significant.

Recent studies demonstrated that NLR can be used as a marker of disease, but it may also predict the disease severity and a poor prognosis (9,10,11,15,19). Similarly, positive correlations were found among the

initial NLR, the initial Hughes scores, and the length of hospital stay. However, it was expected that patients with a high HGS would have a long hospital stay. There was a 1.44-point average improvement after treatment. NLR at presentation showed a significant negative correlation with an improvement in the Hughes scores. Thus a high NLR may be correlated with a slow recovery. Also, the NLR values of IVIg treatment-resistant patients were higher regardless of the disease severity.

Especially in the axonal form, more cranial nerve involvement and a more rapid and severe need for mechanical ventilation was reported (20). In our study, patients with the axonal form had higher HGS at initiation and discharge.

Despite the current positive correlation with disease severity and NLR, there were no significant differences between subgroups. This may be due to different pathogenesis of subtypes of disease.

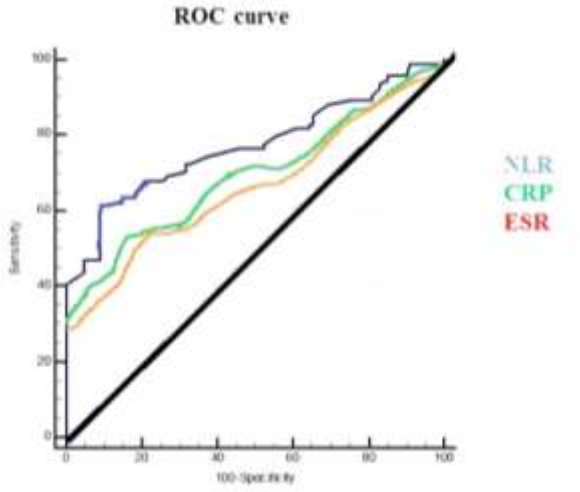

Figure 1.The ROC curve analysis of NLR, CRP and ESR for predicting GBS.

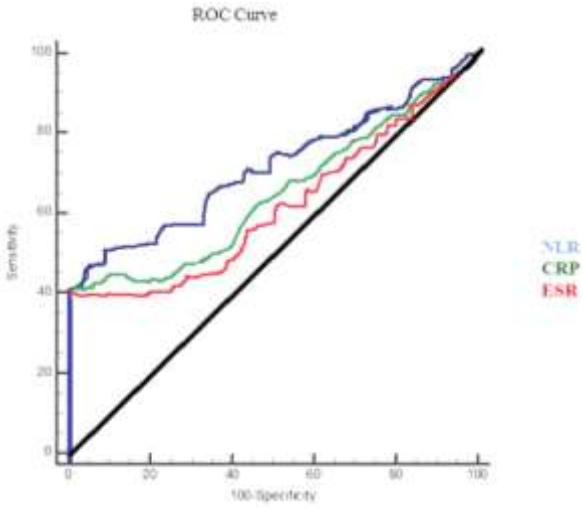

Figure 2.The ROC curve analysis of NLR, CRP and ESR for predicting GBS without infection.

Conclusion

Our study has several limitations. This study used a retrospective design and a small sample size. A major limitation of our study was the failure to obtain follow-up blood samples from all patients at a prespecified time point because they differed in the time of admission and transport to the emergency room. Nevertheless, to the best of our knowledge, the present study is the first to investigate the relationship between NLR and GBS. Unlike ESR and CRP, NLR might be a promising marker in GBS, regardless of infection. Another value, the average for NLR, is an inexpensive, quick and easy measure to obtain, and it might be associated with the severity of the disease..

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

Acknowledgement: Role of Authors:: SG, HB, MN conceived and designed the study;. SG, RY and HB were responsible for data acquisition. SG, HB, MN, SaK, RY and SeK were in charge of data analysis and interpretation and drafted the manuscript. MN and SG were responsible for critical revision of this manuscript. All authors approved the final version of this manuscript.

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http://www.medscidiscovery.com
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ISSN: 2148-6832

MSD Medical Science and Discovery
2016; 3(8):312-6

Original Article Doi: 10.17546/msd.19700

Seasonal effects of the monoamine oxidase inhibitor deprenyl but not the tricyclic antidepressant imipramine in rats bred for helplessness

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Abstract

Objective: Seasonal variations in monoaminergic function may underlie seasonal affective disorder, a subtype of major depression. Here, we examined whether antidepressant drugs which regulate monoaminergic function exhibit seasonal effects in an animal model of depression, congenital helplessness.

Material and Method: Rats selectively bred for helplessness were required to press a lever to turn off a foot-shock before and after chronic treatment with the tricyclic antidepressant imipramine (10 mg/kg) or the monoamine oxidase inhibitor deprenyl (10 mg/kg). Control rats received saline. Different groups of rats were tested in summer-fall and spring over the course of two years.

Results: Congenitally helpless (cH) rats that were treated with imipramine pressed the lever more often than controls in fall and in spring, indicative of antidepressant effects regardless of season. By contrast, cH rats treated with deprenyl pressed the lever more often in summer-fall than in spring, suggestive of seasonal drug effects on helplessness behavior. Deprenyl significantly attenuated the lever-pressing deficit in both seasons when compared to saline controls. Moreover, cH rats treated with deprenyl but not imipramine increased the number of lever presses over trials, indicative of negative reinforcement learning.

Conclusion: The present data are the first to show seasonal variations in antidepressant drug effects that are possibly linked to changes in dopamine neurotransmission. The data support the view that we must take seasonality into account when evaluating the efficacy of antidepressant compounds.

Keywords: Learned helplessness, animal models, depression, antidepressant drugs, biogenic monoamines, negative reinforcement, learning

Introduction

Seasons differ in the lengths of their photoperiods. Starting July, the hours of daylight progressively shorten until late December when they begin to lengthen again. Some humans are susceptible to these changes and show symptoms known as seasonal affective disorder (SAD), a subtype of major depressive disorder. Although rodents are nocturnal animals (they are awake and active when it is dark), they also appear to respond to changes in photoperiod. C57BL/6J mice showed higher levels of immobility in the forced swim test, indicative of behavioral despair, when they were exposed to short as opposed to long hours of light (1).

Even rats housed under standard lab conditions with a regular 12:12 light/dark period exhibited seasonal changes in behavioral despair; levels of immobility were lower in August and November than in February and May (2).

An abundance of evidence implicates the serotonin (5-HT), norepinephrine (NE) and dopamine (DA) systems in the regulation of seasonal rhythms and the pathophysiology of SAD (3,4). For example, serotonin transporter (SERT) binding was found to vary with season (5,6), and both SERT and dopamine transporter (DAT) binding were reduced in patients with SAD (7,8).

Levels of 5-HT and DA varied with photoperiod in diurnal and nocturnal rodents (9), and following light deprivation markers for apoptosis were increased in monoaminergic neurons, particularly in noradrenergic neurons of the locus coeruleus (10). Here we asked whether antidepressant drugs exhibit seasonal effects given that the underlying neurobiological systems on which they act undergo seasonal changes.

Received 08-07-2016 **Accepted** 21-07-2016 **Available Online** 15-08-2016
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Specifically, we compared the efficacy of the tricyclic antidepressant imipramine and the monoamine oxidase (MAO) inhibitor deprenyl across seasons in a congenital rat model of depression. model is based on selective breeding of rats that exhibit a helpless phenotype in a behavioral paradigm (11-14). We hypothesized that both imipramine and deprenyl show a seasonal variation with regard to their efficacy in attenuating helplessness. Imipramine binds to the SERT and the norepinephrine transporter (NET) and increases the levels of 5-HT and NE in the synapse by blocking their reuptake.

Deprenyl is a selective irreversible MAO-B inhibitor at low doses and, thus, enhances DA neurotransmission by inhibiting the breakdown of DA (15,16). Deprenyl exerts antidepressant effects at high doses at which the specificity for MAO-B is lost and both MAO-A and MAO-B become inhibited to increase 5-HT, NE and DA (17,18). Thus, any differences in seasonality between imipramine and deprenyl would implicate the DA system specifically, and any differences related to the drugs' specific mechanisms of action.

Material and Methods

Subjects

We employed naïve male 4-10 months old congenitally helpless (cH, n = 59) rats. The rats were bred at Brookhaven National Laboratory (Upton, NY, USA), where the experiments took place. The animals were derived by selective breeding of wild type Sprague-Dawley rats based on behavioral outcomes in a learned helplessness paradigm (11,12).

The rats were housed in pairs in standard polycarbonate cages and maintained on a 12:12 light:dark cycle (lights on at 7.00 am). They had free access to food and water. All procedures were approved by the Institutional Animal Care and Use Committee of Brookhaven National Laboratory and were conducted in accordance with the Guide for the Care and Use of Laboratory Animals.

Selective breeding

The original protocol for selective breeding was developed by Vollmayr and Henn (19), and was slightly altered by Schulz et al. (12). In short, Skinner boxes equipped with grid floors were employed to deliver altogether 20 min of uncontrollable and unpredictable foot-shock. The next day, the animals were tested for learned helplessness by exposure to 15 foot-shocks that lasted 60 s unless turned off earlier by one lever press.

Rats were classified as helpless when they turned off the foot-shock within 20 s on 5 or fewer trials. Males and females of this category were selectively bred for over 50 generations.

Drugs

Imipramine and deprenyl hydrochloride were purchased from Sigma Aldrich (St. Louis, MO, USA). The drugs were dissolved in 0.9% saline and administered intraperitoneally (i.p.) in a volume of 1 ml/kg at a dose of 10 mg/kg. Control groups received saline.

Procedure

In the present study, cH rats were exposed to helplessness tests only because impairments are present in this strain even without prior exposure to uncontrollable stress (12-14). Test 1 was conducted as a baseline test. The rats were exposed to 15 escapable foot-shocks according to our standard testing protocol. The following day, drug treatment commenced. The animals received imipramine, deprenyl or saline once daily for 14 days. The next day, the animals were re-tested for helplessness (Test 2) using the same protocol as before.

The two days after that, the animals were tested for helplessness again (Test 3 and Test 4, respectively). Drug treatment continued on the re-test days, unless otherwise specified. The injections took place at least 60 min after the behavioral test. Lever presses were automatically recorded by Graphic State software (Coulbourn Instruments, Allentown, PA). For each animal, we analyzed the number of lever presses which turned off the foot-shock within 20 s of shock onset. The experiments were carried out over the course of 2 years in summer and fall (July and November) and in spring (April – May). Rats treated with deprenyl in July (n = 4) and November (n = 5) did not significantly differ from each other in the number of lever presses (all Ps > 0.05), and were therefore pooled (n = 9). Rats treated with deprenyl in spring were also similar, including one batch (n = 5) that was treated for 14 days but not during the re-test days (all Ps > 0.05), and were therefore pooled (n = 15). One batch of animals was treated with imipramine in fall (n = 5) and another in spring (n = 5). cH rats treated with saline in fall (n = 10) and in spring (n = 15) served as controls for the drug-treated groups

Statistical analysis

All data used for statistical evaluations were checked for normality and equal variance of the distributions, using the Shapiro-Wilks test and Levene-statistic, respectively. Results did not allow for parametric testing to be used in all cases.Accordingly, group comparisons were performed using the Kruskal-Wallis H-test. If statistical differences were revealed ($P < 0.05$), the Mann-Whitney U-test was carried out for post-hoc comparisons. To compare repeated measures within a group, Friedman tests were applied.

Results

Overall group comparisons revealed that the groups differed from each other in Test 2 ($P < 0.001$), Test 3 ($P < 0.001$), and Test 4 ($P < 0.001$), but not in the baseline test ($P = 0.75$). Post-hoc comparisons showed that rats injected with imipramine in fall did not differ from rats injected with imipramine in spring (all Ps > 0.05), although imipramine-treated rats performed better than saline-treated controls in fall (Test 2: $P = 0.01$; Test 3: $P = 0.3$; Test 4: $P = 0.001$) and in spring (Test 2: $P = 0.02$; Test 3: $P = 0.06$; Test 4: $P = 0.008$; Fig. 1a). Lever-pressing performance did not significantly increase over the test trials in imipramine-treated rats (fall: $P = 0.19$; spring: $P = 0.26$).

By contrast, rats treated with deprenyl in summer-fall turned off the foot-shock more often than rats treated with deprenyl in spring (Test 2: $P = 0.005$; Test 3: $P = 0.06$; Test 4: $P = 0.03$), indicative of a seasonal drug effect (Fig. 1b). Compared with saline, treatment with deprenyl significantly increased the number of lever presses in fall (Test 2: $P < 0.001$; Test 3: $P = 0.005$; Test 4: $P = 0.001$) and in spring (Test 2: $P = 0.01$; Test 3: $P < 0.001$; Test 4: $P < 0.001$). Moreover, deprenyl increased the number of lever presses across trials in fall ($P < 0.001$) and in spring ($P = 0.05$).

Rats treated with saline in fall did not differ from rats treated with saline in spring (all Ps > 0.05). In fall, the number of lever presses were similar across trials ($P = 0.25$), and in spring performance decreased over the trials ($P = 0.01$).

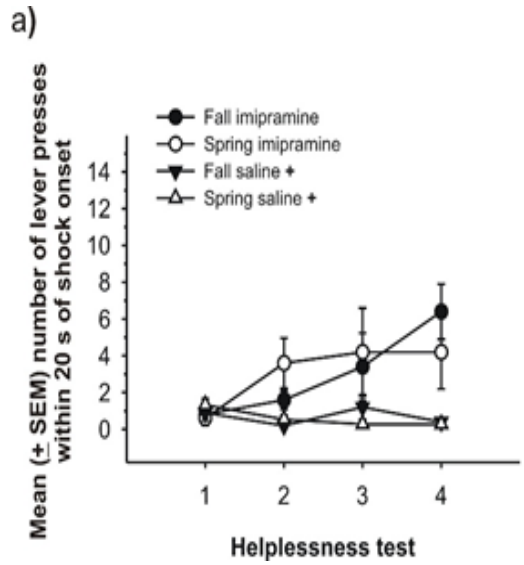

Figure 1. Seasonal variations in antidepressant drug effects. **a)** Effect of the tricyclic antidepressant imipramine (10 mg/kg) on mean (+ SEM) number of lever presses within 20 s of shock onset in fall and in spring. Imipramine was equally effective in both seasons, but was superior to saline in treating helplessness behavior.

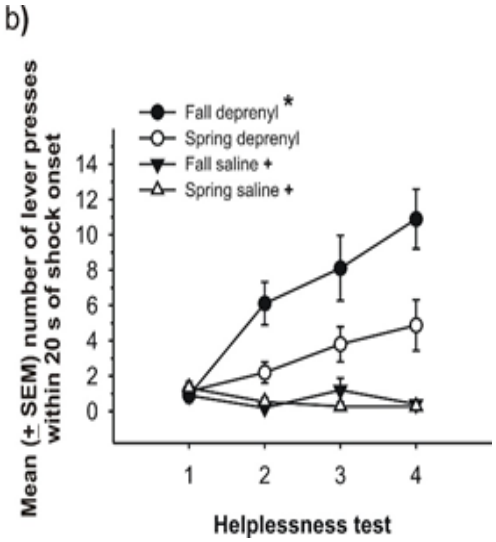

Figure 1. Seasonal variations in antidepressant drug effects. **b)** The monoamine oxidase inhibitor deprenyl (10 mg/kg) was more effective in summer-fall than in spring to increase the number of lever presses that turned off aversive foot-shock, indicative of a seasonal drug effect. Compared to saline, deprenyl attenuated helplessness behavior in both seasons. +drug vs. saline control; *deprenyl in summer-fall vs. deprenyl in spring.

Discussion

In summary, we found that deprenyl was more effective in summer-fall than in spring to reverse a lever-pressing deficit indicative of helplessness, although deprenyl clearly attenuated the deficit in both seasons. Imipramine was equally effective in improving the lever-pressing deficit in fall and in spring. In both seasons, lever-pressing performance increased over trials indicative of negative reinforcement learning in rats treated with deprenyl, but not in rats treated with imipramine.

Although several studies have reported seasonal variations of static measures, such as levels of 5-HT (20), SERT binding (5,6), and even platelet [3H]imipramine binding (21-23), few studies have observed seasonal variations of dynamic measures, such as physiological and behavioral responses to drugs. In one study, seasonal effects of intravenous L-tryptophan, the precursor of 5-HT, were shown on serum prolactin and plasma tryptophan levels with prolactin entering a trough and tryptophan peaking in the middle of the year (24). Interestingly, Joseph-Vanderpool et al. (25) showed that SAD patients gave higher ratings on the activation/euphoria item of the NIMH self-rating scale when the 5-HT agonist meta-,

chlorophenylpiperazine (m-CPP) was administered in winter as compared to summer. Here, we show for the first time a seasonal drug effect of deprenyl in an animal model of congenital depression. Deprenyl was more effective in treating congenital helplessness in summer-fall than in spring, while it was effective compared to saline in both seasons. By contrast, imipramine was similarly effective in attenuating helplessness in fall and in spring.

Differences in seasonality between the drugs could also directly relate to differences in the drugs' mechanisms of action. Imipramine binds to the SERT and NET to inhibit the reuptake of 5-HT and NE into the cell, whereas deprenyl binds to MAO to inhibit the breakdown of monoamines.It is surprising that imipramine did not exhibit seasonal variations in its effects on helplessness behavior in light of the many findings that implicate the 5-HT system in circannual rhythms. We cannot exclude that the lack of effect is related to the specific animal model used, drug dose or other method-related differences. Few reports have examined the seasonal rhythmicity of MAO, and they do not conclusively point to the enzyme as key in mediating seasonality.

In humans, platelet MAO was not related with SAD (30). In rats, circadian variations of MAO-A and MAO-B were observed in the brain stem (31), and in mice, components of the circadian clock were found to regulate the expression of MAO-A which, when reduced, led to an increase in striatal DA (32).

Previous work has shown that immobility in the forced swim test, indicative of behavioral despair, was lower in summer-fall and higher in spring (2). The present data show that helplessness was attenuated by deprenyl to a greater extent in summer-fall compared to spring. This could indicate that a) deprenyl is most effective in summer-fall or b) helplessness is less fixed or rigid in summer-fall, and therefore easier to treat. In support of the former, patients with SAD showed a greater responsivity to the 5-HT agonist m-CPP in winter compared to summer (25).

Lastly, we observed that cH rats treated with deprenyl but not imipramine improved their lever-pressing performance across trials, indicative of negative reinforcement learning (12). DA is known to play a prominent role in reinforcement learning, and it has been suggested that reinforcers and DA could promote operant learning through a direct action on memory traces (33-35).

This implies that DA might play a role in the treatment of congenital helplessness, possibly via actions on negative reinforcement learning processes.

Conclusion

The present data are the first to demonstrate seasonal effects of deprenyl in the attenuation of helplessness, and most strongly implicate the DA system in these effects. The data support the view that we must take seasonality into account when evaluating the efficacy of antidepressant compounds.

It remains to be seen whether seasonal drug effects can also be found in other animal models of depression, and whether such effects are present with other drug classes, e.g. glutamatergic drugs.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues: All Authors declare that originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

Aknowledgement: The research was conducted at the former Medical Department of Brookhaven National Laboratory, NY, USA. DS conceived of the experiments, collected and analyzed the data, and wrote the manuscript. DS was supported by BNL LDRD 10-023 to Congwu Du and Yeditepe University. The author declares no conflicts of interest. I would like to thank Fritz Henn and the Medical Department for providing rats and support.

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ISSN: 2148-6832

MSD Medical Science and Discovery
2016; 3(8):317-9

Case Report Doi: 10.17546/msd.13557

Endovascular therapy of isolated internal iliac artery aneurysm

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Abstract

Isolated internal iliac artery (IIA) aneurysms are relatively uncommon. Isolated IIA aneurysms traditionally have been treated by surgical reconstruction. We report our experience with endovascular treatment of isolated IIA aneurysm.

Key words: Iliac Aneurysm; Endovascular Procedures; Vascular Grafting

Introduction

An isolated aneurysm of the IIA is relatively uncommon and is generally asymptomatic. It is often diagnosed in a late stage and it carries a high rupture risk. We describe our experience of an isolated IIA aneurysm case that we treated with a branched stent-graft, which is in general a rarely performed procedure

Case Report

A 57-year-old male patient presenting with pain in his right thigh underwent CT angiography which showed an aneurysmatic dilatation of nearly 40 mm in a 6 cm segment of the right common iliac artery to the proximal regions of the iliac arteries. The widest part of the dilatation showed the presence of a nearly 20 mm thrombus. The left common iliac artery showed an aneurysmatic dilation of a nearly 3 cm segment reaching proximally, with a maximum diameter of 18 mm where a 2 mm thrombus was seen.

Via a right femoral arteriotomy a sheath was placed including a stiff guidewire that was led to the thoracic aorta. A second guidewire was then inserted in a retrograde manner to the terminal aorta and was guided out of the vessel at the left femoral level using a cross-over approach.

The distal end of the stent-graft main body was placed to cover the aneurysm proximally and to appropriately guide the IIA. The guidewire that was taken out of the vessel by a cross-over approach and via a left arteriotomy was used to lead the vascular sheath to the proximal end of the stent-graft at the aortoiliac level.

The distal end of the vascular sheath that was inserted via a left arteriotomy, was placed at the level of the stent-graft main body. The sheath was then used to lead the guidewire through the internal iliac branch of the stent-graft main body.

Via a left femoral approach, the guidewire was led through the internal iliac branch of the stent-graft main body and was placed in the right IIA where the internal iliac limb was positioned.

Discussion

A systematic review of studies of the autopsy from both North America and Europe showed that the incidence of isolated iliac aneurysms varies between 0.03% and 0.1% 1,2,3 as compared with 3.8% for abdominal aortic aneurysms.3

Because of the deep pelvic location it is difficult to diagnose isolated iliac artery aneurysm on physical examination and it likely accounts for the high incidence of symptomatic or ruptured aneurysms in the past. 4 Today, most of iliac artery aneurysms are usually detected as an incidental finding during diagnostic imaging while searching for other suspected conditions.

Endovascular management has offered the ability to deal with the challenges of deep pelvic structures with minimal morbidity with perioperative mortality rates approaching 0%.5,6,7

Received 28-06-2016 **Accepted** 01-07-2016 **Available Online** 15-08-2016
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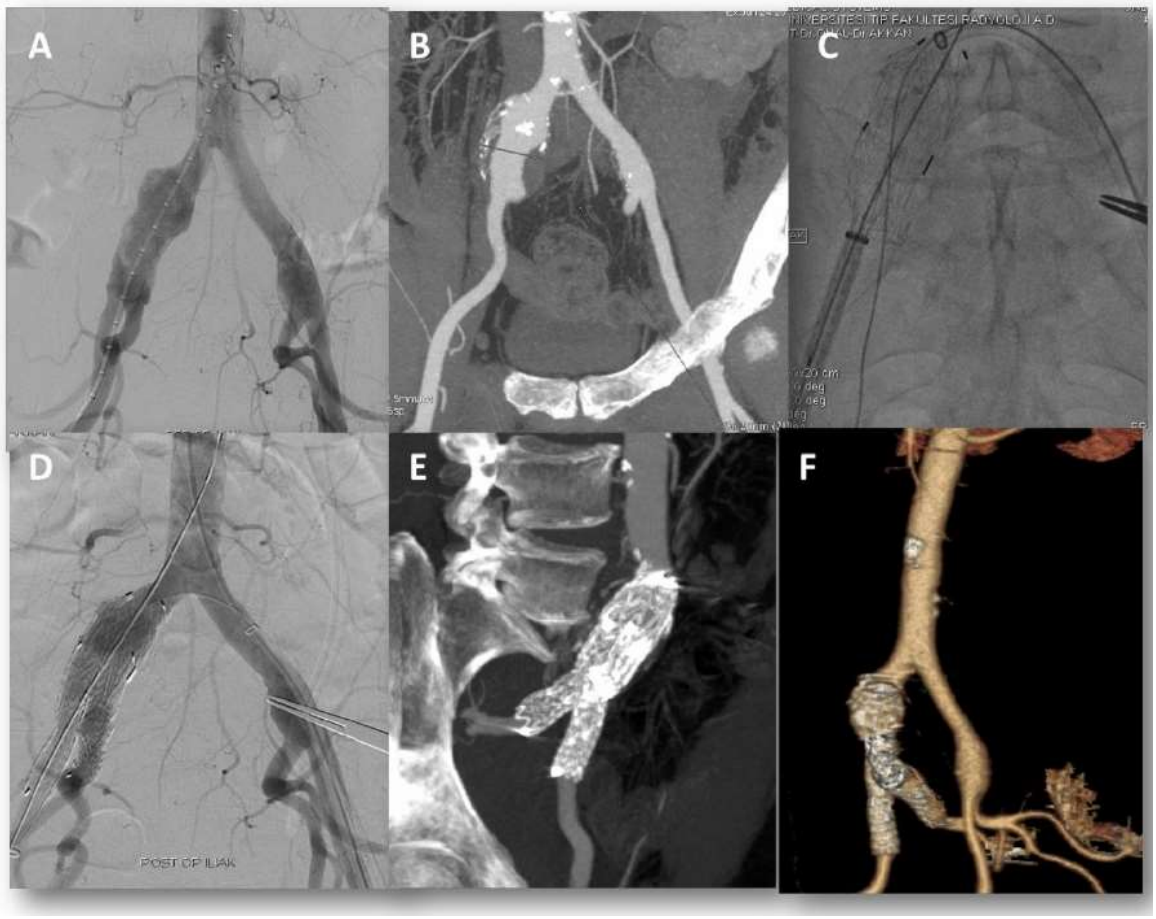

Figure 1: A, B: Aneurysmatic dilatation of nearly 40 mm in a 6 cm segment of the right common iliac artery **C:** Positioning of branched stent-graft **D:** Postoperative DSA **E:** Postoperative MIP CT **F:** Postoperative 3D CT

Conclusion

Treatment of an isolated IIA aneurysm with a branched stent-graft is a rarely performed procedure with a low morbidity rate and a high success rate, and it led to a symptomatic improvement in our case.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

Aknowledgement: None.

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MSD
MEDICAL SCIENCE & DISCOVERY
ISSN: 2148-6832
Lycia Press LONDON UK

International Journal of
Medical Science and Discovery
Open Access Scientific Journal
August 2016, Vol.3, No.8
www.medscidiscovery.com