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Chronic Diseases Journal

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1. Perlman AI, Sabina A, Williams AL, Njike VY, Katz DL. Massage therapy for osteoarthritis of the knee: a randomized controlled trial. Arch Intern Med 2006; 166(22): 2533-8.

2. Buckwalter JA, Marsh JL, Brown T, Amendola A, Martin JA. Articular cartilage injury. In: Robert L, Robert L, Joseph V, editors. Principles of Tissue Engineering. 3rd ed. Burlington, MA: Academic Press; 2007. p. 897-907.

3. Kuczmarski RJ, Ogden CL, Grammer-Strawn LM, Flegal KM, Guo SS, Wei R, et al. CDC growth charts: United States. Advance data from vital and health statistics. No. 314. Hyattsville, Md: National Center for Health Statistics, 2000. (DHHS publication no. (PHS) 2000-1250 0-0431)

4. World Health organization. Strategic directions for strengthening nursing and midwifery services [online]. Available from: URL:http://www.wpro.who.int/themesfocuses/theme3/focus2/nursingmidwifery.pdf2002

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Table of Contents

Original Articles(S)

Case Reports(S)

Short Communication(S)

Chronic Diseases Journal

Nurses' strategies in prevention of nursing error recurrence in chronic critical care: A qualitative study

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Original Article

Abstract

BACKGROUND: Nursing errors are common in critical care units while most of them are preventable. Critical care nurses are uniquely positioned to prevent the recurrence of nursing errors. The purpose of this study was to explore the strategies considered or used by nurses in order to prevent the recurrence of nursing errors in chronic critical care units.

METHODS: A qualitative design using content analysis method was employed in the present study. In-depth interviews were conducted with a sample of 17 participants, recruited through purposive sampling. This study was conducted in 2011-2012 in Iran.

RESULTS: Results indicated that the strategies used by critical care nurses to prevent recurrence of nursing errors include personal strategies (paying more attention, updating information, reminding and hinting, experience sharing, prevention), and expectations from the organization (increasing intrinsic motivation and decreasing work pressure).

CONCLUSION: Nursing administrators must be aware of the individual strategies used by the nurses to develop and promote their implementation and underlying these strategies. Identifying and understanding the strategies used by nurses can help them in their support provision. Explored strategies can be used to develop interventions for prevention of nursing errors. Further exploration of the question of how the nursing context will influence strategy selection and why is necessary. Regarding the strategies used by nurses, nurse managers must utilize them in planning in order to develop an error free care.

KEYWORDS: Nursing Error, Critical Care, Strategy, Content Analysis

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Introduction

Errors in health care are of great importance, since they may have noncompensable consequences.[1] As a matter of fact, nurses and all health care providers inadvertently commit errors in their practice.[2] In addition, nursing errors will increase the time interval of staying at the hospital which can be stressful for both patients and nurses.[3] Currently, clinical errors are addressed as a significant social issue and concerns about them are growing.[4]

Nursing errors can occur at any point of the nursing process, in the form of an action or actions which have a negative impact on patient safety or quality of care.[5] Nursing errors in critical care units mostly occur due to further need of patients for nursing cares.[6] Patients in critical care

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suffer from a life-threatening condition that requires constant monitoring and comprehensive care. Some of these patients improve from an acute status into chronicity while in the critical care units. Chronic critical illnesses account for approximately 6% to 10% of all patients treated in the critical care units, annually; however, recent studies show that this percentage is increasing. They often experience recurrent episodes of instability, a need for prolonged medical and nursing care, multiple-organ dysfunction or failure, ongoing need for life-sustaining interventions, and uncertain trajectory for recovery. Outcomes for patients with chronic critical illness are associated with a high risk of disability, distress, and death. Therefore, they need more precise care and are more disposed to nursing errors.[4,7] However, it has been stated that the majority of errors are never reported, and about half of them are considered as preventable.[8,9] Consequently, considering the inevitability and preventability of nursing errors particularly in critical care units, the main question is: 'What are the strategies considered or used by nurses in preventing the recurrence of nursing errors in chronic critical care?'.

Henneman et al. reported that nurses use different strategies to identify, prevent, and correct medical errors in critical care units and they play a pivotal role in the recovery from medical errors and ensuring the patients' safety.[10] In another study, nurses used surveillance, anticipation, double checking, awareness of the big picture and experiential knowledge to identify medical errors in an academic emergency setting.[11] Frith et al. mentioned nurse staffing as an important strategy to prevent medication errors in community hospitals.[12] In previous studies, there is little information about the personal strategies that critical care nurses use to prevent the recurrence of nursing error in critical care units. Moreover, their identification, which has been neglected until now, is important for prevention of nursing errors in critical care. Therefore, we planned and conducted this study to explore strategies used by nurses to prevent nursing error recurrence in critical care units.

Materials and Methods

With regard to the aim of this research, a qualitative research design with a content analysis approach is used which offers instruments for examining experiences and results in the acquisition of valuable and in-depth data from participants.[13,14] The present study was conducted in 2011-2012.

Purposive sampling, by considering the maximum variation, was used to recruit nurses who were working in chronic critical care and had at least one year of work experience in critical care units of hospitals which are affiliated to Tehran and Kurdistan Universities of Medical Sciences, Iran. Participants were recruited from three urban hospitals in two provinces of Iran. Attempts were made to seek participants with a variety of ages, of both genders, and work experience in critical care. The participants consisted of 17 critical care nurses (Table 1).

First, written informed consents were obtained from all participants. Data was collected through deep semi-structured interviews. The interviews with 17 critical care nurses were conducted in Persian and continued until completion of data collection and theoretical saturation. The principal researcher managed the member checking. Interviews were conducted for 6 months. Each interview was held within 30 to 60 minutes, recorded on the tape, and its content was immediately transcribed on paper and then analyzed. The interview took place at the first meeting, and the second was done in order to resolve an ambiguity in the first interview and for member check. Interviews, depending on the preference of the participants, took place either in the hospital or nursing department. We used main and probing questions to acquire an in-depth understanding of the experiences of the participants. For example: Please tell me about your experience of nursing errors?; What do you do to avoid them happening again?; What should

Table 1. Demographic characteristics of the participants

Participant	Gender (male/female)	Age (year)	Work experience (year)	Work experience in critical care (year)	Center
1	F	30	5	3.0	Tehran
2	M	43	11	7.0	Tehran
3	F	45	15	3.0	Tehran
4	F	34	7	6.0	Tehran
5	M	35	8	5.5	Tehran
6	M	32	8	7.0	Tehran
7	M	28	2	1.0	Tehran
8	M	29	10	6.0	Kurdistan
9	M	25	2	2.0	Kurdistan
10	F	29	7	7.0	Kurdistan
11	M	42	16	16.0	Kurdistan
12	F	46	23	12.0	Tehran
13	F	43	16	5.0	Kurdistan
14	M	32	12	9.0	Tehran
15	F	38	14	12.0	Kurdistan
16	F	35	13	10.0	Kurdistan
17	F	44	18	15.0	Tehran

Table 2. An example of category development

Meaning units	Primary code	Subcategory	Main category
"They must motivate their staff so that they can focus on their work, and not to burst somebody's bubble."	Motivating	Intrinsic motivation	Expectation from organization
"Value and cost are important for critical care nurses, they should be distinguished from the nurses who work in general wards!".	Distinguishing		
"… I think organizations should reduce the working shift of nurses as much as possible…"	Pressure reduction	Decreasing work pressure	
"… Organizations should supply enough staff to reduce work pressure, especially during the night shifts…"	Reducing pressure of night shifts		

we do to prevent the recurrence of nursing errors?. Hence, the participants were asked to present other points which came to their minds and had not been addressed during the interview.

Qualitative content analysis was used to analyze the data; the qualitative content analysis is beyond mere word counting and is one of the common research methods for analyzing textual data.[15] Following data transcription, inductive content analysis, defined by Elo and Kyngas, was used.[15] This process includes three stages of open coding, creating categories, and abstracting. In open coding, notes and headings are written down while reading the text; consequently, they are read completely and the required number of headings is transcribed in the margin of text, and categories are created freely in this stage. After open coding, the list of categories fitting to higher level headings is classified. Abstraction means formulating a general explanation of the research subject through creating categories. Each category is named according to its lexical content. Subcategories are classified in a similar manner and they form categories which are similarly classified as the main categories. The abstraction process was pursued to the extent that was logical and possible.[15] An example of category development is presented in table 2.

This study was approved by the research committee of the Tehran University of Medical Sciences and the administration of each hospital. Consent forms were obtained from all voluntary participants, especially for recording their voice. The participants were assured that they could

leave the study at any time and their names and other significant details that might reveal their identity would not be published in the study report. All names were converted into codes during the transcription of the interviews, data locked in separate locations, and the coded information was used for data analysis and discussion.

Strategies were used in this study to demonstrate scientific trustworthiness, based on the criteria set in qualitative nursing references.[13,14] In order to increase the reliability of the data in the present study, these points were taken into account: allocation of an appropriate place and adequate time for collecting the data; suitable relationship with the participants; using the complementary views of the colleagues; going over the handwritten materials for the participants and examining the data by all researchers for increasing the acceptability of encoded data. The research was conducted by a PhD candidate of nursing with clinical experience in critical care nursing, and was supervised by an associate professor. In order to verify the findings of the data, the supervisor rechecked all the stages of transcribing the interviews, coding, and development of categories. Whenever different codes emerged, the raw data were examined in the presence of the research team until they reach an agreed code.

Results

The final analysis revealed the strategies that prevent nursing errors for participants. The strategies which were identified from the interviews and confirmed with participants are helpful in avoiding nursing error recurrence. Strategies used by nurses are classified as personal (paying more attention, updating information, reminding and hinting, experience sharing, and prevention) and expectations from the organization (increasing intrinsic motivation and decreasing work pressure).

Expectation from the organization

The main part of the views of the nurses about prevention of error was that they expect the organization to make some changes. They expected the organization to increase their intrinsic motivation and decrease their work pressure.

Intrinsic motivation

Increasing intrinsic motivation was one of the major expectations of the participants in order to deliver an error free care. Participant 6 stated: "They must motivate their staff so that they can focus on their work, and not to burst somebody's bubble". Participant 7 stated: "Also, financial incentives are very important…value and cost are important for critical care nurses, they should be distinguished from the nurses who work in general wards!".

Decreasing work pressure

Another important expectation of nurses was the reduction of work pressure via the organization. Participants 6 mentioned that: "We have an important role in preserving patients' life, so I think organizations should reduce the working shift of nurses as much as possible; if this was done, nurses would pay attention to their patients and not to their hard shifts!".

Personal strategies

One of the important aspects of strategies used to prevent nursing errors is personal strategies and includes paying more attention, updating information, reminding and hinting, and experience sharing.

Paying more attention

Paying more attention to care was one of the main strategies used by nurses in prevention of recurrence of the same or similar errors by nurses. For example, one of these strategies was about drugs. In this respect participant 1 stated: “First, I see that the new vial of ranitidine made by the new medicine factory was the same as the other drugs, so we labeled it with a red marker to prevent medication error by nurses in the next shifts". Another aspect of paying more attention by nurses was considering different criteria for decision making. Participant 2 stated: "… there are many criteria for judgment, but no one criteria is sufficient. We should spot clinical and other

criteria before procedures; then, decide on the care delivery method for prevention of errors". Another technique to pay attention was thinking of procedures before performing them. In this respect, participant 4 said: "…when I do something like that in patients, I think of the process and the steps, until the error does not occur".

To update information

Another aspect of the participants view about prevention of error recurrence was updating information. Updating was possible by studying, searching in databases, taking retraining courses, or questioning of colleagues. Participant 17 declared: "Because I've just come from another ward, I study and will increase my information about new procedures and care. Now I've changed and I'm better". Participant 7 stated: "Studying is important. I think the best way to prevent medication and nursing errors is studying!". Moreover, participant 14 said: "…we should improve our information… must increase our understanding about patients and their disease".

Reminding and hinting

Reminding was one of personal strategies used by participants for prevention of nursing errors. Nurses prevent nursing errors by reminding their colleagues and physicians of the patient's situation. Participant 1 "For example, I tell the doctor that the patient has diabetes and has taken dexamethasone for two weeks. So, his/her blood sugar would not be controlled." Hinting was another strategy used by nurses. Participant 7 stated: "The first time, one of the nurses hinted that TNG should be based on monitoring the patients rate, so I hinted this point to other nurses because it stuck in my mind."

Experiences Sharing

Most participants pointed out the issue of personal strategies by gaining experience and sharing them with others. Participant 16 said: "Well, I remember my error, I gained an experience… however, it resulted in me not repeating this mistake again". Participant 1 also stated in this respect that: "For example, about that patient, that I told you about, I was very sad and I told my friends about it so that they apply further precision in the same patients…". The experience sharing was utilized to prevent the recurrence of the same errors by participants and their colleagues. Participant 5 stated: "… I try to tell the story in any way to my colleagues until they know and will not do it in the same way…".

Prevention

Participants in this study emphasized the importance of prevention of error recurrence and they thought it necessary. In this respect, participant 4 stated: "…The best option for an error not to occur is prevention…because it has more consequences! ...So, prevention is better than to cover the errors; it is easier, less costly, and with less psychological pressure…". Participant 8 also stated: "…We have patients in critical situation; so, you must think of this situation and prevent the possible errors of this situation…".

Discussion

In the view of the participants, organizational and personal strategies could prevent recurrence of errors. Expectations of nurses from the organization consist of increasing intrinsic motivation and reducing work pressure, and personal strategies include paying more attention, updating information, reminding and hinting, sharing experiences, and prevention.

The occurrence of medical errors is inevitable; therefore, health care providers need to focus on optimizing the system to reduce errors.[16] The participants mentioned that important solutions to prevent errors through their organization was to increase intrinsic motivation and decrease work pressure. Organizational factors are considered as key factors in error occurrence and reporting errors.[17] There are two approaches to the problem of human errors including personal approach and system approach. Personal approach concentrates on the errors of individuals, blaming them for indiscretion, inattention, or moral weakness. System approach focuses on circumstances where the person works

and tries to build a line of defense against errors and reduce their complication.[18] Therefore, nurse managers should adopt a systematic approach to identifying the work conditions of critical care nurses, and take action to prevent or mitigate the effects of errors.

Note that the errors seem to be caused by inappropriate mental processes such as inattention, poor motivation, omission, negligence, and thoughtlessness.[18] Therefore, nurse managers should try to motivate critical care nurses in their work and care delivery. Based on previous studies, increase in motivation can increase the incentive to keep working and pay attention to patients' safety. Kudo et al. showed that nurses' motivation for preventing errors had a relationship with certain factors of safety climate such as reporting, nursing conditions, and communicating with physicians.[19] Nursing managers should take steps to avoid errors while identifying motivating factors for the prevention of errors by nurses.

Another organizational factor in prevention of errors from the prospect of the participants was decreasing work pressure. According to the nurses' perception, work load was one of the factors underlying nursing errors, thus reducing their work load was introduced as a strategy to prevent their errors. The current shortage of nurses has led to a considerable work burden being placed on the nurses, and the possibility of error is higher and patients are more vulnerable in the critical care units.[20,21] Consequently, fatigue and work pressure can lead to increment in error of nurses in critical care units.[22] Therefore, reducing nurses' work pressure can lead to an improvement in patient safety.[1] In the study of Toruner and Uysal, 19.3% and 16.8% of nurses, respectively, mentioned that low nurse-to-patient ratios and reducing work hours are effective in the prevention of medication errors in pediatric wards.[23] Therefore, nursing managers should provide adequate human resources, comply with the standards of nurse to patient or nurse to bed, and must reduce workload of nurses in critical care units.

The main point in personal strategies was their view about the importance of prevention. They tried to achieve this goal by increasing their accuracy in performing the procedures, updating their Information, reminding and noting the status of their patients to themselves, colleagues, or physician, and sharing their experience with others.

Paying attention is important in care delivery and especially in drug administration. Factors such as fatigue of care provider, distraction in drug administration, inadequate lighting, and deterioration of patient acuity can affect medication errors. Furthermore, distractions and interruptions can disturb the clinician's concentration and lead to severe mistakes.[24] Therefore, factors that reduce the attention of critical care nurses in care delivery should be identified and eliminated. One of the methods of care is patient-centered care that is accompanied by an increase in accuracy and is effective in improving quality and safety of patient care.[25] Another study determined that strategies like surveillance are used by nurses as a strategy for prevention of nursing errors. Surveillance includes continuing acquisition, interpretation, and synthesis of data about patients for clinical decision making. Surveillance differs from monitoring in purpose and scope. Monitoring is an essential activity in the process of surveillance, but monitoring is insufficient for conducting effective surveillance.[26] Therefore, considering that one of the activities of critical care nurses is patient monitoring, nursing managers can develop this behavior of surveillance for prevention of nursing errors.

One of the other personal strategies of critical care nurses for preventing errors was to update their information. Lack of knowledge has been discussed as one of the most common causes of medical errors.[27] In the study of Toruner and Uysal, nurses reported that having sufficient information about the safe use of drugs was one of the important methods for avoiding medication errors.[23] Moreover, studying and updating information, especially about new drugs, can

reduce the chance of medication errors.[24] Updating information has an individual aspect; nurses seek their information personally. Furthermore, they considered educational courses to be effective. Subsequently, nurse managers in addition to providing educational courses, which are appropriate for nurses' needs, should also prepare and provide personal references (such as new references, software, and educational materials in critical care units), and obtain the ability to respond quickly to nurses' informational needs in confronting different situations.

Participants mentioned reminding and hinting about patient situations for themselves, colleagues, or doctors as a personal strategy. Patient care is teamwork and interprofessional communication has a relationship with patient safety and medical errors.[28] Furthermore, nurses have a crucial role in the health care team because nurses are in permanent contact with patients, in contrast with all other members of the caring team who do not stay beside the patients after visiting them.[29] The establishment of interprofessional communication can lead to gaining more information about the patient's situation for all the health care team members, and thus, prevent recurrence of nursing errors.

Overall, there are different strategies for the prevention of errors such as checklists, interdisciplinary rounds, clinical information systems, and clinical decision making support systems.[26] These strategies can be used, but nursing managers must further explore the reasons of errors and orientations about strategic options, and utilize the appropriate strategies for the current status of critical care units.

It should be remembered that the generalizability of the findings of the study is limited due to its qualitative design and small sample size in critical care units. Therefore, it is recommended that more studies be undertaken for further exploration of nurses' experience in choosing and using strategies for prevention of nursing error recurrence. Moreover, more studies are required for further exploring certain strategies such as reminding and hinting and sharing experiences. In addition, more studies are needed to explore nurses views about strategies that they think should be implemented by their organization and administration.

Conclusion

In this study the considered or used strategies of critical care nurses to prevent nursing errors were explored. Considering the inevitability of nursing error, one of the most appropriate methods to select strategies for preventing errors in addition to exploring the view of nurses is to identify the strategies used by them. As a result, strategies applied by nurses would be accepted and implemented by them more easily. These strategies could be appropriate for development and implementation. Identifying and understanding the strategies used by nurses can help in providing support for them. Hence, explored strategies could be used to develop interventions for preventing nursing errors. Further exploration of how the nursing context effects strategy selection and its reasons are necessary. Therefore, with regard to the strategies used by nurses, nurse managers must plan to create an error free care.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

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Chronic Diseases Journal

Diagnostic value of high sensitivity C-reactive protein levels in dedifferentiation of stable angina from unstable angina

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Original Article

Abstract

BACKGROUND: Differentiation of stable angina from unstable angina is important because they need different approaches. Few studies have been conducted to assess the diagnostic value of high sensitive C-reactive protein (hs-CRP) in differentiating these two diseases. This study aimed to evaluate the diagnostic value of hs-CRP levels for differentiating stable angina from unstable angina.

METHODS: After signing the consent form, patients with unstable angina who referred to Tohid Hospital emergency in Sanandaj, Iran, and patients with stable angina who referred to the special clinic of the hospital were evaluated. Disease was confirmed by a cardiologist. Morning serum hs-CRP was tested using MONOBIND laboratory kit (USA). Data were analyzed by SPSS using Student's independent t-test, Mann-Whitney U, chi-square, Fisher exact test, and receiver operating characteristic curve.

RESULTS: hs-CRP levels in patients with stable angina and unstable angina were 1.6 (± 1.18) and 2.35 (± 1.30) mg/l, respectively (P = 0.025). The hs-CRP level ≥ 2.31 mg/l was the best cut-off point for differentiating stable from unstable angina. At this cut-off point, the sensitivity and specificity were 56% and 73%, respectively. Area under the curve was calculated to be 0.679 (95% confidence interval: 0.54-0.81) (P = 0.017).

CONCLUSION: hs-CRP level is helpful for differentiating patients with stable angina from those with unstable angina. It is recommended to consider the hs-CRP level of 2.31 mg/l as the best cut-off point.

KEYWORDS: Acute Coronary Syndrome, Stable Angina, Unstable Angina, Diagnostic Test, Receiver Operating Characteristic Curve

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Introduction

Inflammation is a common component of atherosclerosis and is a likely cause of rupture in atherosclerotic plaques. Inflammatory proteins have been investigated in several studies as a biomarker of atherosclerosis.

High sensitive C-reactive protein (hs-CRP) is one of the biomarkers that have been used widely.[1-5] In patients with acute coronary syndrome (ACS), hs-CRP above 3 mg/l may be associated with a worse prognosis. However, some other studies have not confirmed the association between this biomarker and prognosis of the disease.[6-13]

In addition, some studies have assessed the diagnostic value of this biomarker in diagnosis of ACSs including stable angina, unstable angina, and stroke; in some cases, it was proved as useful diagnostic tool[14-16] while other studies showed

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contrary results.[16,17] Hence, its efficiency is controversial, and there is a need for further researches. Differentiation of stable angina from unstable angina is important because they need different treatment procedures; however, there is a controversy about the efficiency of hs-CRP for differentiating stable from unstable angina.[17-20]

Since some previous studies have shown that increased level of hs-CRP worsens the prognosis, [10,11,18,21] the assessment of diagnostic value of this biomarker for differentiating these two diseases can be clinically valuable because it can simultaneously indicate the prognosis of the disease.

It is of great importance for clinicians to determine a cut-off point for diagnostic tests. Receiver operating characteristic (ROC) curve analysis is a method for determining the cut-off point. In this method, a curve is plotted for every point of diagnostic test valve to calculate sensitivity and specificity. Hence, this curve can present the diagnostic test's efficiency for the classification of patients.[22]

Therefore, this study aimed to examine the diagnostic value of hs-CRP levels and to determine the sensitivity and specificity of different levels of this biomarker in the differentiation of stable angina and unstable angina.

Materials and Methods

Using convenience sampling, patients with unstable angina were selected among those who referred to Tohid Hospital emergency in Sanandaj, Iran, due to chest pain, and patients with stable angina were selected among those referred to the special clinic in Tohid Hospital. Stable angina and unstable angina were confirmed by a cardiologist.

This study was approved by the Ethics Committee of Kurdistan University of Medical Sciences and the purposes of the study were explained to patients and informed consents were obtained. Fasting blood samples were collected from all patients in the morning at the early time of attending the hospital. Exclusion criteria included the presence of infectious diseases in the past 3 weeks, the immune system and autoimmune disease, recent surgery in the past 2 months, a history of trauma in the past 2 months, renal failure, liver failure, cancers, and the use of anti-inflammatory drugs.

Considering differences between averages, having $\alpha = 1\%$, $\beta = 10\%$, and average hs-CRP levels of 1.7 (± 0.9) mg/l for stable angina group versus 0.93 (± 0.9) mg/l for unstable angina group, the sample size was calculated to be 22 patients in each group;[15] in this study, 30 patients were included in each group. All the patients filled a questionnaire which included their past records; in addition, to measure CRP, blood samples were tested using MONOBIND (Monobind, Inc. Lake Forest, CA, USA) laboratory kit, made in USA.

Data were entered in SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). The quantitative data in the two groups were compared using Student's independent t-test or Mann-Whitney U test, and the qualitative data were compared using chi-square and Fisher exact test. To determine the CRP cut-off point, ROC curve was used, and the specificity and sensitivity were determined at the cut-off point.

Results

A total of 60 patients, including 30 patients with stable angina and 30 patients with unstable angina were studied. From all, 24 patients (40%) were female. Mean age of patients in the stable angina and unstable angina groups were 62.1 ± 14.3 and 59.7 ± 12.9 years, respectively (P = 0.5). Among them, 16 (26.7%) patients were from rural areas and the rest were from urban areas. A total of 20 patients (33.3%) had a history of heart attack in their family. Twelve patients (20%) were smokers; 18 patients (30%) had a history of hypertension, 9 patients (15%) had a history of diabetes, and 17 patients (28%) had a history of hyperlipidemia. Apart from that blood pressure, which was higher in the unstable angina group (P = 0.024), the other variables were similar between the two groups and there was no statistically significant difference (Table 1).

Table 1. Comparison of characteristics of patients in the two groups of unstable angina and stable angina

Variables	Stable angina	Unstable angina	P
Sex			
Male, n (%)	19 (63.3)	17 (56.7)	0.790
Female, n (%)	11 (36.7)	13 (43.3)	
Residency			
Urban, n (%)	20 (66.7)	24 (80.0)	0.380
Rural, n (%)	10 (33.3)	6 (20.0)	
Family history of MI, n (%)	8 (26.7)	7 (23.3)	0.410
Current smoker, n (%)	5 (16.7)	7 (23.3)	0.740
Passive smoker, n (%)	7 (23.3)	6 (20.0)	0.754
HTN, n (%)	5 (16.7)	13 (43.3)	0.024*
Hyperlipidemia, n (%)	6 (20.0)	11 (36.7)	0.250
Diabetes, n (%)	2 (6.7)	7 (23.3)	0.140**
Age (year)	62.1 ± 14.3	59.7 ± 12.9	0.499***
BMI	26.4 ± 4.9	26.5 ± 3.5	0.991***
hs-CRP (mg/l)	1.6 ± 1.18	2.35 ± 1.3	0.025*,***
Smoking (pack/year)	5 (0.15-32)	19 (0.45-100)	0.268€

* Statistically significant;** Fisher's exact test was applied; *** Independent t-test was applied; € Mann-Whitney U test was applied; Other comparisons were done by chi-square test; MI: Myocardial infection; HTN: Hypertension; BMI: Body mass index; hs-CRP: High sensitive C-reactive protein

hs-CRP levels in patients with stable angina and unstable angina were 1.6 ± 1.18 and 2.35 ± 1.30 mg/l, respectively, and the difference was statistically significant (P = 0.025). A hs-CRP level ≥ 2.31 mg/l was the best cut-off point for differentiating stable from unstable angina. In this cut-off point, the sensitivity and specificity were 56% and 73%, respectively (Figure 1). With a level of 2.31 mg/l, the area under the curve was calculated as 0.679 (95% confidence interval = 0.54-0.81) (P = 0.017). Table 2 shows sensitivity and specificity of some hs-CRP levels for differentiating stable and unstable angina.

Discussion

In this study, the baseline characteristics of the two groups were similar. Compared with stable angina group, hs-CRP level in patients with unstable angina was higher. The best cut-off point to differentiate unstable angina from stable angina was calculated as 2.31 mg/l. Therefore, hs-CRP seems to be helpful in differentiating stable angina from unstable angina.

Differentiating stable from unstable angina is important because these two diseases need different processes and different approaches to be treated, and also there is no specific biomarker for differentiating these two. In this study, we concluded that to differentiate these two diseases we have to set a cut-off point. There are few studies that have assessed the diagnostic value of this biomarker in differentiation of stable and

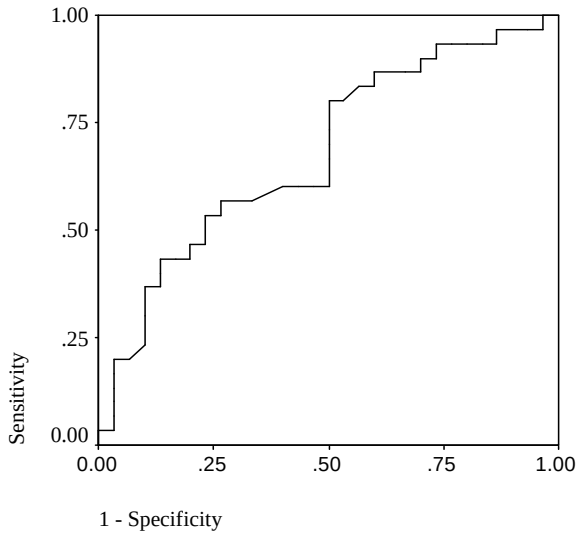

Figure 1. Receiver operating characteristic curve for differentiating unstable angina from stable angina; The area under the curve in a level of 2.31 mg/l was calculated as 0.679 (95% confidence interval = 0.54-0.81) (P = 0.017)

Table 2. Calculated sensitivity and specificity of high sensitive C-reactive protein levels for the differentiation of stable angina from unstable angina

hs-CRP (mg/l)	Sensitivity	Specificity
0.130	1.00	0.03
0.205	0.96	0.06
0.265	0.96	0.13
0.320	0.93	0.13
0.450	0.93	0.16
0.555	0.93	0.20
0.615	0.93	0.26
0.750	0.90	0.30
0.815	0.86	0.30
0.885	0.86	0.40
0.970	0.83	0.43
1.065	0.80	0.50
1.220	0.70	0.50
1.310	0.66	0.50
1.420	0.60	0.50
1.560	0.60	0.53
1.740	0.60	0.56
2.025	0.60	0.60
2.250	0.56	0.66
2.310†	0.56	0.73
2.360	0.53	0.73
2.415	0.53	0.76
2.495	0.46	0.80
2.615	0.43	0.80
2.745	0.43	0.83
2.860	0.43	0.86
3.035	0.36	0.86
3.235	0.30	0.90
3.320	0.23	0.90
3.545	0.20	0.93
3.745	0.20	0.96
3.940	0.16	0.96
4.120	0.13	0.96
4.250	0.10	0.96
4.355	0.06	0.96
4.445	0.03	0.96
4.540	0.03	1.00
5.560	0.00	1.00

† The best diagnostic level; hs-CRP: High sensitive C-reactive protein

unstable angina. One of the studies showed that the best time for taking biomarker samples from patients with stable angina was in the morning, because the biomarker was at its highest level.[21] Based on the mentioned study, the biomarker's level was associated with coronary artery disease and with increasing the severity of coronary artery disease the biomarker's level was increased too. They determined a cut-off point for differentiating patients with severe coronary atherosclerosis based on the mild one which was equal to 5.5 mg/l in the morning with sensitivity and specificity of 66.4% and 79.1%, respectively.[21] In Thakur et al.'s study[4] the hs-CRP levels in patients with coronary heart disease and in healthy subjects were reported as 1.70 ± 0.75 and 0.93 ± 0.35 mg/l, respectively, which showed a statistically significant difference ($P < 0.001$). Some other studies also showed that patients with unstable angina which had higher levels of this biomarker were at higher risk of death and heart failure.[13,18]

In the study by Diercks et al.,[17] patients with chest pain were examined for ACS, and they were also tested to measure their levels of this biomarker. They concluded that this biomarker did not have a diagnostic value in differentiating the two groups. Even so, their study was retrospective and might have had some biases. Another study by Amanvermez et al.,[20] showed that the hs-CRP level in patients with unstable angina was higher than in controls. They also concluded that this biomarker might be useful in early diagnosis of ACS.

Our study had some limitations. We did not assess the relation between this biomarker and cardiac enzymes, electrocardiography changes, and the severity of coronary artery disease. Nonetheless, they were not among the objectives of the study, but assessing them could also present broader information about the biomarker in ACS. However, based on our results, the biomarker levels of 2.31 mg/l and higher show unstable angina while the levels below 2.31 mg/l indicate stable angina. When using this biomarker, the presence of infectious and inflammatory diseases should be considered because they will interfere with the test results.

Conclusion

hs-CRP level is valuable for differentiating patients with stable angina from those with unstable

angina. It is recommended to consider the hs-CRP level of 2.31 mg/l as the best cut-off point.

Conflict of Interests

Authors have no conflict of interests.

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Chronic Diseases Journal

Serum anti-cyclic citrullinated peptide antibodies before and after treatment by disease-modifying anti-rheumatic drugs

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Original Article

Abstract

BACKGROUND: Rheumatoid arthritis (RA) is the most common chronic disease involving joints. Anti-cyclic citrullinated peptide (anti-CCP) as a specific antibody is a reliable index to early diagnosis of RA. Disease-modifying anti-rheumatic drugs (DMARDs) can reduce progression of RA joint destruction. The present study aimed to investigate the effects of DMARDs in reducing serum anti-CCP.

METHODS: A cross-sectional study was performed on 30 patients including 22 females and 8 males RA patients according to the American College of Rheumatology (ACR) classification criteria, who referred to the Rheumatology Clinic. Treatment with DMARD group started at the beginning of the study (May 2009). At 1st and 6th month of the study, clinical findings and disease activities were recorded and anti-CCP was measured.

RESULTS: At the beginning and the end of the study, morning stiffness for more than 1 h and involvement of three areas were, 28 (93%) and 12 (40%), respectively. Indicators of disease severity in patients, the mean ± SD serum levels of erythrocyte sedimentation rate at the beginning and end, were 40.7 (30-59) mm/1 h and 13.4 (9-86) respectively. Anti-CCP at the beginning and end of the study was 141.83 (65.8-101.09) U/ml and 65.8 (62-92) U/ml respectively ($P < 0.05$). Disease Activity Score in 28 joints and rheumatoid factor positive and C-reactive protein positive were significantly different at the onset and at the end of the study ($P < 0.05$).

CONCLUSION: Measurement of serum anti-CCP is a helpful index of treatment response and monitoring of treatment efficacy in patients with RA.

KEYWORDS: Rheumatoid Arthritis, Anti-Cyclic Citrullinated Peptide Antibodies, Disease-Modifying Anti-Rheumatic Drug Group

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease in which the Synovium tissue can be attacked more than any other organs. Despite of increased medical costs, the

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quality of life is impaired in many patients clearly. The American College of Rheumatology (ACR) criteria usually is used for classification of RA,[1] which does help neither early diagnosis nor determination the severity of disease. Laboratory tests can lead to fast diagnosis. Measurement of anti-cyclic citrullinated peptide (anti-CCP) antibodies besides other antibodies such as prinuclease antibodies, anti-cratin antibody, anti-filagrin antibody can confirm the diagnosis.[2,3]

The current blood marker is rheumatoid factor (RF), anti-Fc fragment of IgG, which is neither specific nor sensitive enough for diagnosing RA. RF titer in the early stages of the disease may not be sufficient enough for the diagnosis and disease prognosis. Therefore, treatments based on this finding may not be enough. Finding a marker that indicate rheumatoid arthritis diagnosis at early stages, could be helpful for prognosis and monitoring of responses to the treatment.[4] Citrulline, as an unusual amino acid, is produced by an enzymatic reaction of arginine. It is as a part of the protein building such as filagrin and profilagrin. During cell differentiation process, this protein will be produced. In RA patients, anti-CCP antibodies are synthesized against this atypical protein. Anti-CCP measurement is a method for determining the prognosis of arthritis because it accompanies with more destructive forms of RA. Anti-CCP test has a high sensitivity and specificity and it is checked via enzyme-linked immunosorbent assay (ELISA) and using patients, serum.[5]

Several studies have pointed out the positive predictive value of anti-CCP for prognosis of RA. However, it has also been found in approximately 1.5% of healthy people and in the people with other joint diseases.[6] The disease-modifying anti-rheumatic drugs (DMARDs) group is one of the five group therapies that have been used in the treatment of rheumatoid arthritis. DMARDs including a group of drugs that are structurally uniform. Their common characteristic is slowing down the progression of the disease. They have been accepted as the basis of the treatment of RA.[7] Anti-CCP levels are increasing in early RA disease leading to joint destruction.[8] There are several evidences showing that increased levels of anti-CCP are correlated with progression of radiological joint damage.[9,10]

Several studies have mentioned the relation between serum anti-CCP and DMARD therapy, but they have found some conflicting results.[11,12] disease activity score in 28 joints (DAS28) is a qualitative scale for evaluation of the disease activity and contains four parameters [frequency of swollen joints and joints with tenderness, erythrocyte sedimentation rate (ESR), and visual analog scale (VAS)] and calculated mathematically. Values less than 2.6 were considered as a response to treatment. Anti-CCP in severe forms of RA which can clearly be identified. DMARDs delay progression of the disease.[13]

The present study aimed to investigate the effects of DMARDs in reducing serum anti-CCP. In fact it was designed and performed to address the possibility of if DMARDs interfere in RA pathology by reducing serum anti-CCP as well as application of anti-CCP for monitoring of the responses to DMARD therapy.

Materials and Methods

A cross-sectional study was performed on 30 RA patients who referred to the Clinic of Rheumatology in Towhid Hospital, Sanandaj, Iran. The serum anti-CCP was measured before and after treatment with DMARD group in RA patients.

Duration of symptoms, morning stiffness, number of joints and hand joints involvement, symmetric joint involvement, radiological changes due to RA, rheumatoid nodules, serum RF, ESR, VAS, and anti-CCP and index disease severity scale (DAS28) were also measured and recorded at the beginning of study. From May 2009 to February 2010 (8 months), 51 patients with a primary diagnosis of RA were referred to the rheumatology outpatient clinic. Patients who did not have an acceptable standard or whom refused of performing the experiments or those with medical

complications were excluded from the study.

Based on the American College of Rheumatology (ACR) criteria classification and clinical picture, 30 patients (22 women and 8 men) with diagnosis of RA were recruited. Treatment with DMARD group started at the beginning of the study. At the 1st and 6th month of the study, clinical findings, and disease activities were recorded and anti-CCP was measured.

After giving a simple explanation to patients, a written consent was obtained. Patient characteristics including the initial signs and symptoms of the disease were recorded. Hand radiographies (by radiologists and rheumatologists) was undertaken and recorded according to SHARP score.

Serum titration of anti-CCP and other tests were ordered and performed for free. To avoid errors and reducing the potential difference between the results of tests conducted in the laboratory, a standard kit was used. At the start of study DMARD, 7.5 mg prednisone daily, hydroxychloroquine 200 mg daily and oral methotrexate (10 mg/week) were prescribed.

By using a checklist, the side effects and clinical examination were investigated and recorded. In 2 of 30 patients, methylprednisolone 80 mg was injected intra-articular and in one patient methotrexate was increased to 15 mg weekly and hydroxychloroquine to 400 mg daily due to severe knee arthritis.

Six months after taking DMARDs, serum anti-CCP, ESR, C-reactive protein (CRP), RF, VAS, and hand radiographs were measured once again. Disease severity index DAS28 that shows the severity of pain and inflammation of the patients were calculated at the beginning and the end of the study. The DAS28 includes joint tenderness (0-28), number of swollen joints (0-28), and ESR. The VAS method was calculated by Excel software. This method is used for pain quality determination and is stated as a horizontal line from 0 to 10 cm long (0 means no pain and 10 means the most intense pain felt by the patient).

Of all 30 patients with RA, 10 cc of blood was taken and serum was separated for testing. Collected samples were transported as frozen to the Unity Center of Immunology Laboratory in hospital. RF was measured via latex agglutination method by using commercial kits Genesis® Company. An anti-CCP antibody was measured by using commercial kits Genesis® that measures anti-CCP antibody of IgG class. In this method, the ELISA microplates have been covered with recombinant citrullinated filagrin.

Control samples with known concentration were also investigated to control the accuracy and reliability of standardized tests in parallel and the results were recorded.

McNemar and Bhapkar's test and Spearman Rank correlation test and Mann–Whitney test were used for data analysis. A probability value of 5% was statistically considered significant.

Results

Eligible patients for the present study were 30 individuals including 22 females (74%) and 8 males (26%). The mean age ± SD of subjects was 48.9 ± 9.72 years. The morning stiffness for more than 1 h and involvement of three areas were, 28 (93%) and 12 (40%), respectively.

Involvement of hand joints at the beginning and end of the study was observed in 30 cases (100%). Involving counterparts joints at the beginning and end of the study were 28 (93%) and 3 (10%), respectively. The corresponding rates was 3 (10%) and 1 (3%) for nodule and 25 (83%) and 9 (30%) for RF titer 1^+ ($P < 0.05$).

Mean and standard deviation of ESR's serum levels at the beginning of study were 40.7 and 30.59 and 10.50 ± 9.86 at the end of study. Median VAS score ± interquartile range (IQR) at the beginning and end of the study were 58.17 ± 20.06 and 16.5 ± 8.92 respectively. Moreover, median DAS ± IQR at the beginning and end of the study, were 6.18 ± 0.94 and 3.17 ± 1.42, respectively.

CRP was positive in 21 patients (70%) at the beginning and only in 12 patients (40%) at the end of the study ($P < 0.007$). A total of 30 (100%) patients had theirserum anti-CCP positive (> 18 U/ml). The median level of anti-CCP at the

Table 1. Comparison of American College of Rheumatology criteria in rheumatoid arthritis patients before and after treatment with disease-modifying anti-rheumatic drugs

Variable	At the beginning, number (%)	At the end of 6th month, number (%)	P
Morning stiffness > 1 h	28 (93)	12 (40)	< 0.001
Involvement > 3 area	28 (93)	13 (43)	< 0.001
Involvement of hand joints	4 (100)	4 (13)	< 0.001
Involving of counterparts joints	28 (93)	3 (10)	< 0.001
Nodules	3 (10)	1 (3)	0.470
RF^+	25 (83)	9 (30)	< 0.001
Radiologic changes	29 (96)	8 (26)	< 0.001

Statistical test: McNemar; RF: Rheumatoid factor

beginning and end of the study was 127 and 25 U/ml, respectively (P < 0.001). The mean ± SD of duration of symptoms until diagnosis was 15.73 ± 13.41 weeks. The history and physical exams and supplementary laboratory tests were negative for all 30 patients. DAS28 as a measure of disease activity in 26 cases (86%) was more than 5.1 and in 4 cases (13%) was higher than 3.1. These finding represent the severe and moderate rates of disease activity. At the end of study, 9 of 30 patients treated with the index DAS28 lower than 2.6.

At the end of 6th month, a significant association was observed between low serum anti-CCP and low ESR, low CRP, lower VAS, and a decrease in DAS28 (P = 0.001). Majority of patients (97%) had an abnormal serum anti-CCP level while this proportion was 85% in RA (Tables 1-4).

Table 2. Changes in Disease Activity Score in 28 joints in rheumatoid arthritis patients before and after treatment with disease-modifying anti-rheumatic drugs

At the beginning	After 6 month				
	Rem	LDA	MDA	HDA	Total
Rem	0	0	0	0	0
LDA	0	0	0	0	0
MDA	1	1	1	1	4
HDA	8	11	5	2	26
Total	9	12	6	3	30

P < 0.001; Rem: Remission; LDA: Low dose activity; MDA: Moderate dose activity; HDA: High dose activity; Statistical test: Bhapkar's test

Table 3. Association between Disease Activity Score in 28 joints and other parameters of disease activity in rheumatoid arthritis patients after 6th month

Parameter	Rho	P
RF	0.43	0.016
ESR	0.30	0.081
CRP	0.27	0.205
VAS	0.002	0.521
Radiologic changes	0.22	0.239

Statistical test: Spearman Rank correlation test; RF: Rheumatoid factor; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; Anti-CCP: Anti-citrullinated cyclic protein, VAS: Visual analogue acales

Table 4. Association between anti-cyclic citrullinated peptide levels and positive rheumatoid factor before and after of treatment in rheumatoid arthritis patients

Parameter	RF^-	RF^+	$Anti\text{-}CCP^+$	$Anti\text{-}CCP^-$	Total
RF^-	5	0	-	-	5
RF^+	16	9	-	-	25
$Anti\text{-}CCP^+$	-	-	19	11	30
$Anti\text{-}CCP^-$	-	-	0	0	0

P = 0.0002; Statistical test: McNemar; RF: Rheumatoid factor; P = 0.0025; Statistical test: McNemar; Anti-CCP normal: < 18 U/ml; Anti-CCP Abnormal: > 18 U/ml; Anti-CCP: Anti-cyclic citrullinated peptide

Discussion

In the present study, a clear reduction in the symptoms was observed and most patients showed a good response to treatment over 6 months. These findings are consistent with other studies.[12-14]

For all patients, the early indicators of disease activity were significantly decreased by treatment with a DMARD group. Previous studies have

reported similar findings. However, decreasing the DAS28 has not been mentioned in these studies.[12-14]

For all 30 patients included in the present study, the anti-CCP had decreased significantly. In the Ronnelid et al. study a reduction in the serum anti-CCP on sulfasalazine was found at the 1st year only.[13] In the Mikuls et al. study, the RF level, but not the anti-CCP level was decreased significantly ($P \leq 0.010$).[14] Through, in the other study, serum IgM, but not anti-CCP was reduced significantly.[15,16]

According to the entering criteria for the study, all patients had unusual serum anti-CCP at the beginning of the study. At the end of study, due to drug intake 10 patients became RF negative. But anti-CCP was detectable which reflects the greater specificity of the anti-CCP. During the course of treatment, the RF in 11 patients became negative, but serum anti-CCP level was still higher than the normal values.

At the beginning of study, none of patients were RF positive and anti-CCP was lower than normal, but in all 30 RA patients who had ACR87 criteria, the anti-CCP levels were higher than normal. At the end of the study, there was only one positive RF with anti-CCP levels lower than normal. But at the same time in eight patients with positive RF, there was positive serum anti-CCP. These findings indicate a similar specificity (68%) and more sensitivity (89%) of RF compared with anti-CCP ($P < 0.050$), as shown in other reports.[15-18] This might be due to existing antibodies against heterogeneous citrulline or different epitopes of citrulline molecules. Every patient can produce antibodies of different affinity, while kits are used for identification anti-CCP in the laboratory, consisting limited antigens.

The main limitation of this study was the presence of patients who were taking other drugs, and referred to different clinics. However, they were excluded from the study. Another limitation of the study was the small sample size due to time constraints.

Conclusion

Measurement of serum anti-CCP is a helpful index of treatment response and monitoring of treatment efficacy in patients with rheumatoid arthritis. Early indicators of disease activity could be significantly decreased by treatment with DMARD group. For patients with a suspected RA, along with clinical examination, measurement of anti-CCP levels and the positive rate is recommended. Anti-CCP measurement along with the physical exam and index DAS28 can be useful as indicator in monitoring patients treated for rheumatoid arthritis.

Conflict of Interests

Authors have no conflict of interests.

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Chronic Diseases Journal

Association between plasma homocysteine and diabetic retinopathy in type II diabetes mellitus

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Original Article

Abstract

BACKGROUND: Diabetic retinopathy (DR) is one of the complications occurs in patients with diabetes mellitus (DM) and is the leading cause of new onset blindness. This study aimed to determine the possible association between plasma homocysteine (Hcy) levels and the development and progression of DR.

METHODS: This case-control study enrolled diabetic patients who referred for ocular consultation from the Diabetes Clinic of Tohid Hospital in Sanandaj, Iran, in 2013. Patients with type 2 DM (n = 156) were randomly assigned to evaluate the association between Hcy and DR. Participants were randomly divided into two groups; with or without DR. Patients in both groups were matched for confounding factors. Detection and grading of retinopathy was performed by indirect ophthalmoscopy and fluorescein angiography. Glycosylated hemoglobin (HbA1c) was measured by Enzyme-linked Immunosorbent Assay and fasting plasma Hcy levels measured by chromatography. Plasma Hcy more than 15 µmol/l was defined as hyperhomocysteinemia.

RESULTS: The results showed that there were no significant differences in Hcy levels in diabetic patients with or without retinopathy. Also, we found that there was no association between HbA1c level and plasma Hcy. In addition, data analysis indicates that no association was observed between disease duration and Hcy levels.

CONCLUSION: In conclusion, we found that there was not a significant association between plasma Hcy level and DR in patients with type II DM.

KEYWORDS: Diabetes Mellitus, Diabetic Retinopathy, Hyperhomocysteinemia

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Introduction

Diabetic retinopathy (DR) is one of the complications of diabetes mellitus (DM), and the main cause of new onset blindness among 20-74 years old patients in Western countries.[1,2] The risk of blindness in diabetic patients is 25 times greater than non-diabetic population.[1] According to the literature the prevalence of DR varies from 6.7% to 35%.[3,4] It has been reported that over 60% of patients with type II DM develop retinopathy within one or two decades after diagnosis.[5] DR results from microvascular decompensation beginning with basement membrane thickening, leading to vascular occlusion and eventual neovascularization. The duration of diabetes, poor glycemic control, and hypertension (HTN) are documented risk factors in the development and progression of DR.[6] DR is potentially sight threatening, thus the need to locate more effective diagnostic and therapeutic techniques to reduce

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this problem is obvious. Finding a measurable risk factor may have two advantages; the identification of patients who are at greater risk and decreasing the risk of this sight threatening condition by lowering this risk factor, if possible. Recently homocysteine (Hcy) has received much attention. Hcy is an emerging risk factor for cardiovascular and non-diabetic ocular vaso-occlusive diseases.[3] Evidence has now accumulated showing that an elevated plasma Hcy concentration is a risk factor for vascular disease in both normal patients and those with renal disease. Elevated concentrations may induce endothelial dysfunction or abnormalities of coagulation factors and platelets.[7,8]

Hcy is a sulfur amino acid with a free thiol group, not present in dietary protein. This amino acid is a secondary by-product of methionine from cysteine metabolism. The mechanisms of Hcy pathogenesis in vascular damage are unclear. High Hcy levels can cause endothelial damage, with increased thrombosis and atherosclerosis. Hyperhomocysteinemia has been reported in both type 1 and type 2 DM patients. In patients with type 2 DM, the relation between hyperhomocysteinemia, macrovascular complications and renal disease is not completely understood; however, a higher prevalence of macrovascular complications in diabetic patients with hyperhomocysteinemia is associated with a higher prevalence of renal disease. The relationship between retinopathy and Hcy has not been clarified. Although numerous studies have shown an association between Hcy and DR, the results, thus far, have been equivocal.[9] Some studies support the concept that the hyperhomocysteinemia may contribute to the pathogenesis of retinal microangiopathy and DR.[10-15] According to the above studies and in order to find a reliable factor to predict the risk of developing retinopathy, in this study we were interested to evaluate the possible association between plasma Hcy level and DR in patients with type 2 DM.

Materials and Methods

This case-control study enrolled diabetic patients who referred for ocular consultation from the Diabetes Clinic of Tohid Hospital, Sanandaj, Iran, in 2011-2012. All examinations were carried out at the Department of Ophthalmology at the Kurdistan University of Medical Sciences. According to the previous studies 78 subjects were enrolled in each group.[3] All patients underwent complete ocular examinations that included a determination of visual acuity using the Snellen chart, slit lamp examination, intraocular pressure measurement, and precise fundus examination with fully dilated pupils, using an indirect ophthalmoscope and slit lamp biomicroscopy with a 90 D lens. In cases where exact grading of the extent of retinopathy was possible by indirect ophthalmoscope or slit lamp funduscopy, we performed a fundus fluorescein angiography, and fundus photographs were taken for precise detection of any micro-aneurysms or leaking vessels. All examinations were done by a physician who was blind to the study. The case group (n = 78) composed of those patients with DR, irrespective of grade. For each case individual, we selected a matching control individual from previously examined diabetic patients. The case and control groups were matched according to: age, diabetes duration, HTN, ischemic heart disease (IHD), hyperlipidemia, and smoking status (according to: medical records, laboratory analyses, and cardiologic consultation). We obtained complete medical histories from all participants by conducting interviews and reviewing medical records in the diabetes clinic.

Fasting blood samples were obtained from all case and control subjects in the same manner. Hcy and glycosylated hemoglobin (HbA1c) serum levels were measured by Enzyme-linked Immunosorbent Assay and chromatography using Statfax and Mycocard devices, respectively.

Patients who had undergone laser therapy and any intraocular injections for DR, those

with any retinal diseases that interfered with the grading of DR, any patients with renal dysfunction whose creatinine level was ≥ 1.5 mg/dl, and those who were taking any medications increased plasma Hcy levels.

SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The data are expressed as the mean ± standard error of the mean of 78 persons per group. Student's t-test, chi-square or Kruskal-Wallis was used to analyze statistical significance. P values < 0.05 were considered to be significant in all analyses.

The Ethics Committee at the Kurdistan University of Medical Sciences reviewed and approved the study protocol. Signed informed consent was obtained from each individual.

Results

According to table 1, patients were correctly matched based on age, diabetes duration, hyperlipidemia, IHD, HTN, and smoking status. Data analysis indicates that there were not any significant differences between case and control groups in mentioned criteria.

Table 1. Comparison of variables in case and control groups

Matched variables	Case (%) (n = 78)	Control (%) (n = 78)	P
Hyperlipidemia	51.6	63.2	0.172
IHD	27.6	23.1	0.516
HTN	60.3	52.6	0.333
Smoking	4.3	4.0	0.824

HTN: Hypertension, IHD: Ischemic heart disease

Although the HbA1c level was significantly higher in the case group than the control (P = 0.002) but the results showed that there was not statistical differences in Hcy level between the case and control groups (Table 2). Furthermore, our findings in tables 3 and 4 show that there is not a significant difference between the grade of retinopathy and Hcy or HbA1c levels.

In order to find a possible association between diabetes disease duration and Hcy level the case subjects were divided into five groups including (i) less than 5 years, (ii) 6-10 years, (iii) 11-15 years, (iv) 16-20 years, and (v) more than 20 years. Data analysis indicated that there was no significant difference between disease duration and Hcy level (P = 0.300) (Table 5).

Table 2. Comparison of plasma homocysteine and glycosylated hemoglobin in case and control groups

Variables	Mean ± SD	P
Homocysteine (µmol/l)		
Case	10.65 ± 4.60	0.190
Control	9.78 ± 3.50	
HbA1c		
Case	9.44 ± 2.05	0.002
Control	8.41 ± 1.78	

HbA1c: Glycosylated hemoglobin; SD: Standard deviation

Table 3. Comparison of plasma homocysteine levels and retinopathy grade

Retinopathy grade	Subject	Mean ± SD (Hcy)	P
Mild NPDR	15	9.73 ± 3.62	0.481
Moderate NPDR	7	12.77 ± 2.97	
Severe NPDR	31	10.33 ± 4.07	
PDR	25	11.22 ± 5.93	

Hcy: Homocysteine; SD: Standard deviation
NPDR: Non-proliferative diabetic retinopathy
PDR: Proliferative diabetic retinopathy

Table 4. Comparison of plasma glycosylated hemoglobin levels and retinopathy grade

Retinopathy grade	Number of subject	Mean ± SD (HbA1c)	P
Mild NPDR	15	9.73 ± 1.49	0.516
Moderate NPDR	7	12.77 ± 1.35	
Severe NPDR	31	10.33 ± 2.12	
PDR	25	11.22 ± 2.33	

HbA1c: Glycosylated hemoglobin; SD: Standard deviation
NPDR: Non-proliferative diabetic retinopathy
PDR: Proliferative diabetic retinopathy

Table 5. Comparison between plasma homocysteine level and diabetes duration

Diabetes duration (year)	Number of subjects	Mean ± SD (Hcy)	P
0-5	8	11.17 ± 6.70	0.300
6-10	26	10.07 ± 3.01	
11-15	25	10.08 ± 3.74	
16-20	11	13.38 ± 7.07	
> 20	8	9.90 ± 4.78	

Hcy: Homocysteine; SD: Standard deviation

Discussion

The present study was aimed to evaluate the possible relationship between plasma total Hcy (tHcy) concentration and DR.

Our finding indicated that there was not any significant association between the DR degree and plasma Hcy level while there was a positive association between the presence of retinopathy and the amount of HbA1c (P = 0.002). Furthermore, the results showed that, there was no association between plasma Hcy levels and variables such as HTN, HbA1c, IHD, age, and diabetes duration (except for patients older than 70 years).

According to the literature we found that the association between Hcy plasma level and DR data is controversy.[10-15] Satyanarayana et al. conducted a cross-sectional case-control study to investigate the status of B-vitamins and Hcy in DR. They reported that mean plasma Hcy levels were found to be higher in the diabetic patients compared to normal subjects.[16]

Lim et al. showed that Hcy concentration of blood plasma, vitreous and aqueous in the patients with DR was approximately 30% higher than observed in the control subjects.[17] In addition Goldstein et al. reported that there was a significant elevation in Hcy levels in the non-proliferative diabetic retinopathy and proliferative diabetic retinopathy groups compared to the control group. Their findings have suggested that hyperhomocysteinemia might be associated with DR and partially explained the increased risk of microvascular angiopathy occurs in these patients.[18]

Ganapathy and colleagues used mutant mice with endogenously elevated Hcy levels due to a heterozygous deletion of the cystathionine-β-synthase gene and examined changes in retinal pathology following induction of diabetes. Their finding showed that elevated Hcy levels hastened cell loss in the retinal ganglion cell layer.[19] This was approved by Lee et al. that suggested that hyperhomocysteinemia caused by renal failure is often associated with diabetic nephropathy and retinopathy.[20]

On the other hand, some studies indicated no significant differences were noted in plasma Hcy levels between diabetic and control groups.[21,22] Another research has shown that Hcy levels in diabetic patients with pre-proliferative DR were not higher than the healthy normal group but were higher in the neovascular glaucoma group.[12]

In our study, patients with serum creatinine concentration greater than 1.5 mg/dl and those who were diagnosed with renal failure were excluded. It was a difference of our study with others that supported the idea of a positive relationship between DR and hyperhomocysteinemia. Therefore, we have concluded that in those studies renal failure acted as a confounding factor. In addition, Ozmen et al. showed that elevation of plasma tHcy concentration in type 2 DM is related to deterioration of renal function and diabetic nephropathy.[23] Furthermore, the association between Hcy and severity of kidney disease has been reported.[24] Therefore, we believe that retinopathy may develop simultaneously with nephropathy in the process of developing diabetic microvascular complications.

The low plasma Hcy level in all patients in comparison with similar studies[3,4] that may be related to intake regimen was one of the limitations of the present study. In addition, the main limitation of this study was the use of a cross-sectional design, which prevents determination of temporal direction and, therefore, of causal inference. Although retinopathy risk factors and the most important confounders of Hcy in this population specifically, age, sex, smoking status, and renal status were controlled.

In summary, we found that there was not a significant correlation between plasma Hcy level and DR. Nevertheless, it is necessary to perform more studies to clarify the possible association between Hcy and DR.

Conflict of Interests

Authors have no conflict of interests.

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Chronic Diseases Journal

Relationship between asthma and related factors of birth

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Original Article

Abstract

BACKGROUND: Asthma is the most common chronic disease of childhood that causes disturbance in the physical, emotional, mental health, and different information has been mentioned on its risk factors, including factors associated with birth. Therefore, in this study, the relationship between children asthma and factors associated with birth was studied.

METHODS: This case-control study was performed on 50 children with asthma as the case group and 150 children hospitalized without asthma as the control group (after matched for age and sex) in an age range of 4-14 years old. Information required on factors affecting asthma was recorded for both groups. Data analysis was performed using SPSS for Windows software.

RESULTS: The results of this study showed that the majority of children in the case group were males born through cesarean operation (C-section). A significant difference was seen between two groups in terms of factors such as preterm [odds ratio (OR) = 3.27, confidence interval (CI) 95% = 1.57-6.81] and family history of asthma (OR = 8.50, CI 95% = 4.10-17.60). Regression model of relational variables with asthma show that the family history of asthma was most effective determinant on birth-related factors of asthma.

CONCLUSION: The findings of this study showed that positive family history of the disease and premature-birth in infant correlates significantly and directly with asthma occurrence in children. Thus, it is recommended to make further follow-ups in providing prenatal care and early diagnosis of the disease.

KEYWORDS: Asthma, Children, Birth-Related Factors

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Introduction

Asthma is a chronic disorder of the airways.[1] It is the most common childhood disease that causes physical, emotional, psychological and mental problems in children and concerns the parents.[2]

Nowadays, more than 300 million people around the world suffer from asthma.[3,4] It has been estimated that 4.8 million children around the world are suffering from asthma.[5] The prevalence of asthma among children has increased and its prevalence in different populations has been reported from 1% to over 30%.[4,6] Its prevalence in Iranian children has been reported as 8-12%.[7] It is anticipated that by 2015, the prevalence of asthma symptoms in children will exceed over 15%; a phenomenon that needs more consistent attention and planning.[8,9]

The role of multiple risk factors in causing childhood asthma has been studied including risk factors in childhood, maternal related factors and

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environmental factors.[10] Although in some cases, according to different roles of environmental factors, the risk factors for asthma have been studied at perinatal period, infancy, and childhood.[11]

Different birth-related factors such as gender, method of delivery, neonatal infections, and birth weight are involved in the development of childhood asthma.[12] Short gestation period can also impair fetal development.[13] Some studies indicate an association between cesarean section and asthma.[14] For example, a study in Norway showed that the infants born by cesarean section compared to babies born in the normal way were 50% more likely to develop asthma.[15] Regarding the relationship between breastfeeding and incidence of asthma, different results have been reported and hence that some of them have pointed to protective effects of breastfeeding,[16] and some others have mentioned it ineffective.[17] Of other important risk factors, the positive family history of atopic diseases can be mentioned since it increases the risk of asthma alone as 3-4 times more.[16,18] Other factors include living near industrial plants, maternal history of asthma, and birth weight less than 2500 g, maternal smoking (more than half a pack per day), small house and a large number of family members during the infancy period.[19]

Altogether asthma leaves behind many complications and causes high economic costs,[20] while using prevention methods, 70% of attacks can be prevented.[21] Since many factors can have a role in causing asthma, and the relationship of some of them is still not clear definitely, the researchers carried out this study to investigate the relationship between childhood asthma and birth-related factors in children in Iran.

Materials and Methods

This case-control study was performed since March 2012 to December 2013 on children hospitalized in emergency and internal wards in Besat Hospital, Sanandaj, Iran. The case group included 50 children with asthma (convenience sampling), and the control group included 150 children (convenience sampling), which were selected from children who had been hospitalized due to non-respiratory diseases and other reasons, including growth monitoring or transient viral infections and/or gastroenteritis in the ward. In this study, the case and control groups were matched based on age and gender. The inclusion criteria were 4-14 years of age range and the parents' consent for entering the study for both groups; for the case group, diagnosed as having asthma by a specialist in allergy and immunology and based on results of spirometry. Study exclusion criteria for the case group had any non-asthmatic chronic lung disease. All information was collected based on a questionnaire developed in conjunction with birth relevant factors. After obtaining parents' consent to participate in the study and explanations regarding confidentiality of information, data were collected by questionnaire and through interviews with parents. The questionnaire included demographic information and factors related to birth (age, sex, gestational age, type of delivery, birth weight, duration of exclusive breastfeeding, supplementary feeding time, and birth rank) and maternal factors (age, education level, occupation, and place of living). The questionnaire validity was assessed through content validity. Thus, the questions were provided to 10 pediatricians and nurses, and finally, their corrective and suggestive feedbacks were applied. The tool reliability was measured by Cronbach's alpha ($\alpha > 0.79$) after completing by 20. The findings from studies were analyzed using SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA) software and chi-square test and t-test. The significance level was considered as $\alpha < 0.05$ in this study; quantitative data and qualitative data were expressed as mean and standard deviation and as frequency and percentage, respectively. Finally, to specify more effective determinant of birth-related factors of asthma, a regression model was provided. Asthma's related variables with P-values < 0.2

considered in the regression model in univariate analysis.

Results

The two groups were matched for age and sex. The age mean in the case group and in the control group were respectively as 7.19 ± 3.31 and 7.26 ± 3.30 years old, and in both groups, the frequency of male subjects was higher than female ones, and the chi-square test showed no significant relationship between the two groups. Most studied samples in the two groups had a weight over 2.5 kg at birth, and the majority in case and control groups were developed according to gestational age and the t-test indicated a significantly relationship in this regard (P = 0.001). The cesarean delivery was common in both groups that no significant differences were seen between the two groups. The duration of exclusive breastfeeding in the control group was about 6 months, and in about 3 months for the case group, and supplementary feeding for the age of 3-6 months was longer in the case group. In both studied groups, the incidence rate of first birth had the highest frequency. The mean maternal age at pregnancy period in the case and control groups was as 29.36 ± 7.51 and 30.00 ± 7.50 years, respectively, and no significant differences were observed between the two groups in this regard. No significant differences were seen between the two groups in terms of education and place of residence. Family history of asthma was as 50% in the case group and as 15% in controls, and the t-test was significant (P < 0.001). The adjusted odds ratio (OR) values were calculated for studied parameters, and there was a significant difference between the two groups regarding factors such as preterm [OR = 3.27, confidence interval (CI) 95%: 1.57-6.81] and family history of asthma (OR = 8.50, CI 95% = 4.10-17.60) (Table 1). Considering the significance of the results with regard to the

Table 1. Distribution of studied parameters in case (with asthma) and control groups

	Group	Asthma frequency (%)	Control frequency (%)	OR (CI 95%)	P
Gestational age	Preterm Term	18 (36) 32 (64)	22 (14.70) 77 (85.60)	3.27 (1.57-6.81)	0.0500
Type of delivery	Natural Cesarean	26 (52) 24 (48)	96 (64.00) 54 (36.00)	0.60 (0.32-1.17)	0.1000
Birth weight	Below 2.5 kg Above 2.5 kg	11 (22) 39 (78)	29 (19.30) 121 (80.87)	1.17 (0.54-2.57)	0.4000
Breastfeeding	6 months Under 5 month	19 (38) 31 (62)	35 (49.30) 76 (50.70)	1.60 (0.82-3.06)	0.0500
Supplementary feeding time	From month 4 From month 6	41 (82) 9 (18)	118 (78.80) 32 (21.30)	1.23 (0.54-2.80)	0.9000
Birth rank	First rank Second rank and higher	24 (48) 26 (52)	65 (43.30) 85 (56.70)	1.20 (0.63-2.30)	0.5000
Family history of asthma	Yes No	30 (60) 20 (40)	25 (15.00) 125 (85.00)	8.50 (4.10-17.60)	0.0001
Mother age at pregnancy	Under 18 and over 35 18-35	11 (22) 39 (78)	40 (26.70) 110 (73.30)	0.77 (0.36-1.66)	0.5000
Exposed to cigarette smoke	Yes No	17 (34) 33 (66)	55 (36.70) 95 (63.30)	0.89 (0.45-1.74)	0.5000
Place of living	Urban Village	42 (84) 8 (16)	108 (72.00) 42 (28.00)	2.04 (0.88-4.70)	0.0900

OR: Odds ratio, CI: Confidence interval

Table 2. Regression logistics model of relational birth factors with children asthma

Variables	β	SE	Wald	df	P	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Preterm	1.118	0.425	7.827	1	0.005	3.280	4.229	18.009
Family history of asthma	2.166	0.382	32.267	1	0.001	8.727	1.427	7.540
Place of living	-0.881	0.512	2.959	1	0. 085	0.415	0.152	1.131
Exposed to cigarette smoke	0.684	0.433	2.493	1	0.114	1.982	0.848	4.632

SE: Standard error, Df: Degree of freedom, CI: Confidence interval

relation between the variables of preterm, family history of asthma, exposed to cigarette smoke and place of living with children asthma incidence, a regression logistic model was provided to determine, which of these variables could be a better predictor. It shows that the family history of asthma (β = 2.166) was most effective determinant on birth-related factors of asthma (Table 2).

Discussion

In this study, birth risk factors in children asthma were studied, and the role of birth-related factors investigated. Finally, preterm and family history of asthma were related to the incidence of asthma.

Kiechl-Kohlendorfer et al. believes that susceptibility to asthma is affected by several factors early in the life.[22] The results of this study showed that male gender in line with previous studies was a risk factor for asthma. Asthma is more common in boys than girls before puberty time, and in different studies, a higher prevalence has been reported in boys. [1,9,19,20,22,23] In Iran, Rajaeifard et al. reported the male gender as the most important risk factor for the asthma.[24] Serum immunoglobulin E (IgE) levels in males under 1 year were significantly higher, and a significant association between the risk of persistent wheezing and serum IgE levels has been observed that could explain the increasing asthma rate in males.[25]

In the present study, short gestational age or premature infants in the case group was twice more than the control group. This result is in line with previous studies, which have reported a direct and significant relationship between early occurrence and increased prevalence of asthma.[13,26,27] In other studies, the association between intrauterine lifetime and incidence of asthma did not show any significant difference.[28,29] Preterm birth causes reduced lung maturation, and thereby, increased sensitivity and respiratory diseases,[13] since exposes the infant to complications associated with respiratory system events.[19] Thus, it seems that identifying mothers with high-risk pregnancy and proving special care and appropriate follow-up can help to prevent preterm delivery, which in turn can help reducing the risk of childhood asthma.

In the present study, although the majority of children with asthma were born by cesarean section, but statistical test showed no significant relationship in this regard, which was consistent with previous studies in this area.[30-32] Due to the higher frequency of cesarean in Iranian women, this issue can be explained.[33] In other conducted studies, there was a significant association between delivery by cesarean section and asthma incidence.[28,32,34] In Salam et al. study, 25.13% of patients with asthma were born by cesarean section, which indicated a higher prevalence of asthma in children born through caesarean section.[35] In cesarean delivery, due to more contact with microbes and stimulating the creation of T-cell causing atopic reaction, the prevalence of asthma and atopic diseases is higher.[36] Also, vaginal delivery may reduce the risk of childhood asthma or prevent it.[37] In natural birth delivery, the infants contact with probiotics of the delivery channel and such material make the baby resistant to various allergies and life-threatening infections.[16] In this study, although there was no significant statistical relationship between cesarean rate and asthma, however, providing proper training to encourage mothers for natural birth

delivery can be one of the ways to reduce allergic diseases such as asthma.

Duration of exclusive breastfeeding in the case group was about 3 months that the study was consistent with Kramer et al. study, in which no significant difference was observed in the asthma incidence in case and control children[38] versus, in Bilan and Shiva analysis, in atopic children not nourished with breastfeeding, showed the risk of wheezing has been reported as 5.4 times more.[27] Based on the results of similar studies, with increasing absolute duration of breastfeeding (for at least 6 months), the prevalence of asthma has decreased dramatically.[24,28,39,40] It is believed that the mother milk creates some sort of protection against infections by transferring of IgG.[13,39,40] Despite the lack of statistically significant correlation, the rate of breast-feeding in the first 3 or 6 months of study samples was high that represents mothers higher tendency in both groups, which in turn can cause a lot of benefits.

Although the majority of samples in this study in the case group lived in the city, but no statistically significant relationship was seen between the risk of asthma and the location of residency, which was consistent with Mehrabi et al. study, is in the same region.[41] In other studies, such as Sole et al., the higher prevalence of asthma in urban people than rural has been reported.[42] Such a case, given the lack of industry in the studied region and considering that the air is not polluted, and fine dusts are spreading similarly in urban and rural areas in recent years were common factors in studied subjects, and the lack of relationship could be justified.

In the present study, no significant association was found between having been exposed to cigarette smoke and asthma occurrence that can result from common risk factors in both groups, which is consistent with the results of some studies.[30,43] However, other studies reported that the contact with cigarette smoke is effective on asthma incidence.[12,24,41,44] In this respect, Bilan and Shiva study showed that the risk of asthma development with exposure to secondhand cigarette smoke increases approximately 2-times.[27] Such differences between various studies may be due to different genetic factors influence and environmental factors in the different regions.

In this study, more than half of the children with asthma and only 15% of subjects in the control group had a positive family history of asthma, and the statistical test showed a significant difference between the two groups; such a result is quite consistent with other studies.[12,27] Adkinson et al. considered positive family history as the most important risk factor for asthma regarding atopic diseases.[19] Thus, this emphasizes more on the necessity to pay attention to perfect prenatal cares, avoiding other risk-making environmental factors for asthma development, encouraging the breastfeeding and the need for regular follow-up for early diagnosis of children asthma in such families.

One of the limitations of the study was a low number of samples due to the limited number of patients in the research area. Furthermore, according to the retrospective nature of the study, and the possibility of different biases, especially recall bias, and considering the importance of asthma and its prevalence in children, performing more extensive studies with a larger sample size and cohort planning to determine the relationship between asthma and various other factors, including the type of mother's diet during pregnancy or duration of breast-feeding is recommended.

Conclusion

The study findings indicate birth-related factors such as preterm and family history of asthma were related to the incidence of asthma. Therefore, it seems positive family history of asthma requires a closer follow-up and observation after birth. Furthermore, providing appropriate care in pregnancy could prevent asthma, which should be considered in providing nursing care for mothers and infants.

Conflict of Interests

Authors have no conflict of interests.

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Chronic Diseases Journal

Fahr's syndrome in a patient with no history of the disease: A case report

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Case Report

Abstract

Fahr syndrome which presents with various signs and symptoms has a familial predisposition and is characterized by symmetric calcification of basal ganglia. It may present with neuropsychiatric, extrapyramidal, and cerebellar symptoms. The etiology has not been defined yet. A 38-year-old woman referred to the psychiatric clinic of 5th Azar Hospital, Gorgan, Iran, with neuropsychiatric presentation.

KEYWORDS: Fahr's Syndrome, Psychosis, Basal Ganglia Calcification

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Introduction

Fahr's syndrome is idiopathic calcification of the basal ganglia.[1] Clinical features are important since basal ganglia calcification may be viewed as a secondary finding. Other manifestations are: headache, vertigo, movement disorders, paresis, and stroke such as events, cognitive impairment, psychiatric disorders, pyramidal signals, and seizures.[2] When regions other than globus pallidus are involved pathological calcifications occur.[3] Calcification may occur secondary to abnormalities in calcium metabolism or radiation therapy.[4] Bilateral calcification of basal ganglia can be found both on plain skull X-rays (SXR), in 70-80% of cases associated with hypoparathyroidism, and in necropsy specimens.[5] The syndrome has a sporadic idiopathic form and a familial form, which is associated with progressive mental deterioration and growth retardation chorea, dementia, and dystonia.[6] Another finding is levodopa-resistant Parkinson syndrome.[7] Computerized tomography (CT) make it possible to detect calcifications which otherwise are not noticeable on SXR.[5] For instance, normal SXR was reported in 14 cases of basal ganglia calcification, without any evidence of calcium abnormalities, or neurological disease due to calcification.[7] Furthermore, several reports have described familial Fahr's syndrome.[6] Some literatures have described idiopathic familial basal ganglia calcification without clinical manifestations.[1] An array of clinical manifestations in familial Fahr's syndrome may be presented depending on age, level of calcium deposits in the brain, and due neurological deficit.[1] In general, progressive neurological deterioration may results in disability and death.[8] No cure or typical treatment has yet been

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recognized for Fahr's syndrome and treatment of individual cases have shown that haloperidol or lithium carbonate may relieve psychotic symptoms.[8]

Case Report

A 38-year-old woman referred to the psychiatric clinic of 5th Azar Hospital, Gorgan, Iran, in April 2011 due to headache, anemia, feeling of isolation, self-talk, and excessive movements of the upper limbs. She was hospitalized for further investigation in the psychiatric ward due to the severity of symptoms. Eight months before admission the patient was hospitalized and treated with the electric shock therapy because of symptoms such as depression, suicide attempt, loss of energy and insomnia, and diagnosis of psychotic depression. Then she was discharged after improvement of symptoms with perphenazin prescription and amitriptyline. There was no major problem until about 20 days before the current admission which after discontinuing the medication he had insomnia, headache, and self-talk. The patient complained of continuous non-pulsatile headache in the occipital region without nausea and vomiting. Except one of the patient's brothers who had familial Mediterranean fever, other family members had no history of psychiatric diseases. The patient had severe reduction of intellectual content and auditory hallucinations, cognitive impairment in attention, and concentration. The brain CT scan without contrast injection showed bilateral calcifications in the basal ganglia and left cerebellar (Figure 1). Electrocardiography, calcium, phosphorus, alkaline phosphatase, and albumin were within normal ranges. Ophthalmology consultation was normal. Radiographs obtained from the patients' hands showed no other calcium disorders. According to the above findings, Fahr's induced psychotic syndrome was revealed, and treatment began with perphenazin 16 mg/day about 3 weeks later, pain and auditory hallucinations disappeared completely and patient's cognitive weakness improved. Six months later, patient was on maintenance treatment with no psychotic features.

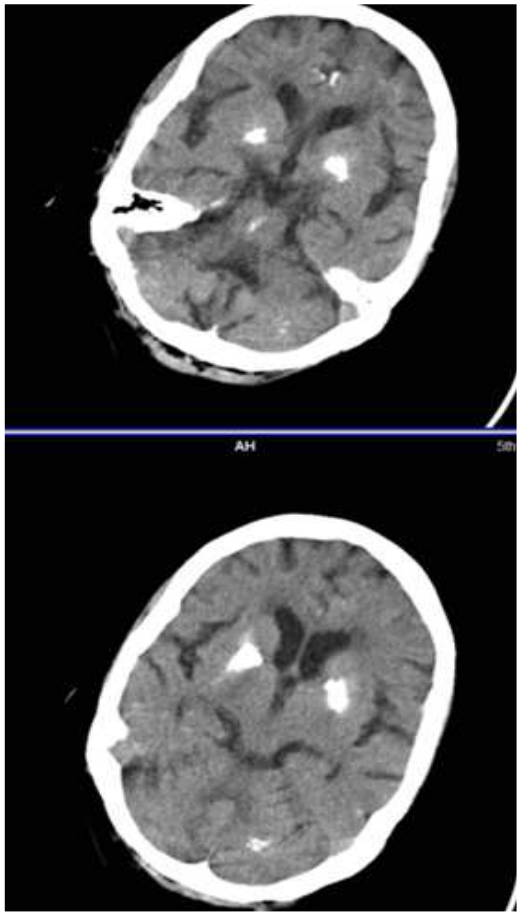

Figure 1. Computerized tomography scan of Fahr's syndrome showing bilateral basal ganglia calcification in a 38-year-old woman

Discussion

Although the etiology of calcification of the basal ganglia is rarely defined, abnormalities in vascular supply, calcium metabolism, and alkaline phosphatase activity appear to be involved. Clinical expression of Fahr's disease (FD) can vary greatly.[2] Patients with basal ganglia calcification may present initially with psychiatric features.[9] In our case, there was no evidence of hypocalcaemia and hyperphosphatemia in the patient. There was no evidence of extrapyramidal symptoms or a metabolic disorder and neurological

examination was normal. However, psychosis can induce differential diagnosis of schizophrenia or acute transient psychotic disorder.[2] Psychiatric presentations including cognitive, psychosis, and mood disorders are common in FD.[9] Other studies indicate the presence of symptoms such as auditory hallucinations, perceptual distortions, and paranoid delusions associated with FD.[9] As in our case schizophreniform psychoses have been reported. Psychosis due to FD responds variably to treatment and is sometimes unresponsive.[8] Imaging diagnosis could be the starting point to guide the clinician for the possibility of Fahr's syndrome.[1,5] The differential diagnosis includes but not limited to: Parkinson's disease, Huntington's disease, progressive supranuclear palsy, Wilson's disease, spasmodic torticollis, oligodendroglioma, low-grade astrocytoma, and arteriovenous malformation.[6] Etiology of Fahr's syndrome is not directly correlated with image calcification pattern, except for some differences noticed in calcifications site in dystrophic senile ones. Topographic image studies are promising to predict neurological deficits. Their recognition by CT is easy, has maximum sensitivity and may be contributing to early treatment.[1]

Conclusion

Our case shows that schizophreniform symptomatology presentations must be investigated in detail with due importance to family history and considering disorders with other clinical manifestations like FD.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

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Chronic Diseases Journal

Wolfram syndrome: A case report

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Case Report

Abstract

Wolfram syndrome (WFS) is a rare disease inherited as an autosomal dominant trait. Type I diabetes mellitus and optic atrophy are the main symptoms of the disease. It is also known as DIDMOAD syndrome due to the association of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness. WFS may be associated with other disorders such as kidney failure, gonadal atrophy, and mental and behavioral disorders. This report is about a 14-year-old teenager who had suffered from vision loss and cataracts when he was 4 years old. At the age of 7 he has been diagnosed with type I diabetes mellitus due to polyuria and polydipsia. At the age of 12 he developed diabetes insipidus, neural hearing loss, urinary incontinence and bilateral hydronephrosis, neurogenic bladder, and increased blood pressure. Physicians should think of this disease and recommend genetic counselling before marriage.

KEYWORDS: Wolfram Syndrome, DIDMOAD, Optic Nerve Atrophy, Hearing Loss, Diabetes

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Introduction

Wolfram syndrome (WFS) is a rarely inherited disease that was first reported in 1938.[1,2] Pedigree analysis has shown that it is inherited through autosomal recessive.[3,4] WFS1 gene that is located on the short arm of the chromosome 4P16.1 is responsible for the disease that is seen in 90% of the patients.[5,6] Its frequency varies in different parts of the world and is about one in 500,000 children. In the UK its frequency is estimated about 1 in 770,000.[5,6] The first and most prominent clinical manifestation is diabetes mellitus and optic atrophy which is usually occurs in the first decade of life.[4] In the course of the disease, most patients suffer from diabetes insipidus and sensorineural hearing loss; hence, it is called diabetes insipidus, diabetes mellitus, optic atrophy, and deafness syndrome (DIDMOAD). In addition to these core symptoms, other disorders such as early cataracts, abnormal optic reflux, nystagmus, renal disorders and neurological complications in the form of ataxia, mental disorders and behavioral and gonadal atrophy could be marked in some cases.[6,7] Most patients eventually develop these complications and 65% of patients die before the age of 35 years.[7-10] Nevertheless, this disease is still not well known.

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Case Report

The patient was a 14-year-old boy who was admitted to the pediatric ward due to diabetes mellitus. The parents were healthy with no

family relationship. In the initial examination, the patient had decreased vision and hearing loss and urinary incontinence. The patient referred to the optician when he was 4 years old due to bilateral visual loss and went under surgery due to cataract. However, the cause of the premature cataract was not investigated further. At the age of 7, the patient was investigated due to polyuria, polydipsia, and urinary incontinence. Then insulin therapy started for him after the diagnosis of type I diabetes mellitus. However, polyuria and polydipsia continued despite insulin therapy. Water deprivation test was done due to low urine specific gravity (SG) and clinical suspicion of diabetes insipidus and after confirming the diagnosis Minirin was started. In recent hospitalization, patient's blood pressure in several assessments was 160/90 mmHg.

In laboratory examination, results blood urea nitrogen = 42, creatinine = 2, and ratio of protein to creatinine in a random urine was about 0.5. Patient glomerular filtration rate was calculated at about 52 using Schwartz formula.

Ultrasound results showed thickened bladder wall revealing coarse echoes of the trabeculae and bladder residual volume was about 150 cc. The patient underwent voiding cystourethrogram to evaluate hydronephrosis with bilateral reflux and distended bladder, the bladder wall was thickened and irregular with bladder diverticulum resulting the improper bladder emptying ending in the diagnosis of neurogenic bladder. Eye examination by an ophthalmologist showed bilateral nerve atrophy. The patient went under tympanometry and audiometry to assess hearing loss. Audiometric pure tone audiometry results showed high frequency neural hearing loss; however, tympanometry results were normal. According to the finding's diagnosis of WFS considered for the patient. Kidney failure in a patient could be related to diabetic nephropathy aggravated by neurogenic bladder and shifting secondary to reflux. Patient's blood sugar and polyuria controlled using insulin and 1-desamino-8-D-arginine vasopressin (DDAVP) spray. Then, the patient discharged after prescribing terazosin and oxybutynin and bladder catheterization training.

Discussion

WFS is an autosomal dominant disorder. The disease is more common in areas of the world where familial marriage is more common. Its prevalence in the world is 1 in 68,000. The first and most prominent clinical manifestation of this disease is diabetes mellitus at an early age. The age of disease onset varies from 3 to 16 years with an average of 6 years. However, our patient age was 4 years.[1,2,7] Diagnosis of WFS in adolescents is possible at an early stage after manifestation of diabetes mellitus and optic atrophy. Premature cataracts have been reported in 29% of the patients as well.[6] In our case, the first manifestation of the disease was occurrence of cataract at the age of 4. Other ocular disorders such as diabetic retinopathy, abnormal light reflex, and nystagmus may also occur.[6] Patients with a wide range of urologic disorders such as reflux and urinary bladder dysfunction have been reported. Urologic disorders may occur in 58% of patients aged 25-10 years with an average age of 20 years.[6] Our case had neurogenic bladder and vesicoureteral reflux. Hearing impairment in WFS is progressive and can be another symptom of the disease.

Neural hearing loss in 60% of the cases is in the high frequencies and occurs in the second and third decades of life with an average age of 16 years. In our patient, tympanomerty was normal, and audiometry results showed hearing loss in high frequencies.[11] In the third and fourth decades with an average age of 30 years, neurological symptoms appear in 62% of patients. The most common symptoms of nerve involvement can be ataxia, loss of smell, dysarthria, hemiparesis, seizures, and nystagmus.[12] In 25% of the cases mental disorders such as psychosis, mood disorders, and depression may be seen. This mental and

physical disorder is progressive and may result in the midlife mortalities.[4,6,13]

Conclusion

Diabetes mellitus is an early manifestation of WFS and late diabetes occurs in the second and third decades of life. Therefore, in cases of diabetes mellitus with early abnormalities such as visual disturbances, hearing disorders, and renal disorders, it is suggested to consider WFS. In cases where there is no family history of diabetes and especially when it is associated with hearing and vision problems or when diabetes autoantibodies are negative one must think of special monogenic forms of the disease. Also, in different parts of the world where consanguinity is more common, such as Iran and other Middle East countries, physicians should consider the disease and recommend genetic counseling before marriage.

Conflict of Interests

Authors have no conflict of interests.

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Chronic Diseases Journal

Prevalence of glucose-6-phosphophosphate dehydrogenase deficiency in the newborns in Sanandaj, Iran

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Short Communication

Abstract

BACKGROUND: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a genetic disorder and assessment of newborns with or without this deficiency is an essential component in public health evaluation in different countries. Hence, this study was aimed to assess the prevalence of G6PD deficiency in the newborn population in Sanandj, Iran.

METHODS: This is a cross-sectional study on 2016 newborns in Besat Hospital in Sanandaj, Iran, in the year 2006. Three drops of blood were collected from the infants' heels using sterile needles. Then fluorescent spot test was utilized to study the activity of G6PD enzyme.

RESULTS: The results of the present study conducted on 2016 neonates showed that 48.80% (984) of them were males and 51.20% (1032) were females. Prevalence of G6PD deficiency in boys and girls were 7.62% and 2.52%, respectively with a male to female ratio of 3:1.

CONCLUSION: G6PD deficiency is a gender related condition with a higher frequency among boys' population.

KEYWORDS: Glucose-6-Phosphate Dehydrogenase Deficiency, Fluorescent Spot Test, Sex Related

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Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is a universally common hereditary disorder. According to World Health Organization (WHO) reports, 2.9% of the world population and 10-15% of the Iranians have G6PD deficiency.[1,2] This disease is more prevalent in Africa, Asia, the Mediterranean, and the Middle East, and approximately 200-400 million people suffer from it all over the world.[3,4]

G6PD enzyme exists in all cells and has a crucial role in providing cell protection during oxidative stress.[5] In individuals with G6PD deficiency, lifetime of these cells is lower than normal due to oxidation of red blood cell membrane; therefore, hemolysis occurs. Moreover, excessive red cell hemolysis and increased catabolism raise blood bilirubin and jaundice.[6]

Main symptoms of defect in G6PD enzyme include acute hemolytic anemia and classic appearance of favism, neonatal jaundice, and non-spherocytic hemolytic anemia.[7] Neonatal jaundice is one of the most important and remarkable symptoms of this deficiency.[8] An important problem of hyperbilirubinemia is irreversible neurological complications and profound mental retardation in the newborns, which are highly prevalent in Greek, Nigeria, Saudi Arabia, and Southern Iran.[4,9] Individuals

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with this deficiency cannot be blood donators. Moreover, prolonged contact with mild cell hemolytic individuals can cause chronic anemia.[10]

Identifying neonates with this enzyme deficiency is highly significant. Different studies from around the world have considered screening of neonates regarding G6PD enzyme as a very effective factor in decreasing Kernicterus. Recent studies on health education in ethnic Kurds revealed a high prevalence of this medical and health risk factors.[11-13]

However, few studies have been conducted on G6PD in ethnic Kurds as one of the Iranian ethnicities and prevalence of the disease in Sanandaj, Iran, has not been identified yet; therefore, detection of the disease would help reduction of side-effects by consuming food and medication containing antioxidants. Hence, the present study was aimed at identifying prevalence of G6PD dehydrogenase deficiency in neonates in Sanandaj.

Materials and Methods

This is a cross-sectional study conducted on 2016 neonates born in Besat Hospital in Sanandaj from 2006 to 2007. Permissions were obtained from neonates' parents. Then three drops of blood collected from the infants' heels using sterile needles after recording of the infants' characteristics.

Fluorescent spot test was utilized to study the activity of G6PD enzyme. For this purpose, 100 µl of reagent put in a small container and 10 µl of whole blood containing ethylenediaminetetraacetic acid were taken from the neonates' feet which was added and mixed afterwards. Subsequently, the solution was kept at the room temperature for 20 min, a drop was taken from it using a 20-µl sampler and put on the filter paper. Then the paper was left out to dry. The resulted spot was put under fluorescent light with the wavelength of 365 µm and its reflected light studied, then the collected data were registered. Samples with G6PD enzyme had the ability to catalyze the chemical reaction, reflect the fluorescent light, and turned into green; however, those with G6PD enzyme deficiency turned into black and could not reflect the light. Data were analyzed in SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA) using chi-square and odds ratio (OR).

Results

The present study conducted on 2016 neonates including 984 (48.80%) males, and 1032 (51.20%) females. Prevalence of G6PD dehydrogenase deficiency was 5.00%, 7.62% in male infants and 2.52% in female. The ratio of male to female in this particular enzyme was 3.02, in addition, chi-square test proved a statistically significant relationship between G6PD dehydrogenase deficiency and neonates' sex (P = 0.0001). The OR was 3.19 (confidence interval 1.98-5.17) (Table 1).

Table 1. Relationship between sex and glucose-6-phosphate dehydrogenase deficiency, in the male and female newborns of Sanandaj, Iran

Sex	With G6PD deficiency, n (%)	Without G6PD deficiency, n (%)
Male	75 (74.3)	909 (47.5)
Female	26 (25.7)	1006 (52.5)
Total	101 (100)	1915 (100)

G6PD: Glucose-6-phosphate dehydrogenase

Discussion

G6PD dehydrogenase deficiency is a sex-related disorder and has different prevalence rates in different countries. In the present study, prevalence of G6PD dehydrogenase deficiency was 5.0%. Its level of prevalence varies in different regions of the country. It has been reported to be 19.3% in Southeastern Iran,[14] 10.9% in Mazandaran,[15] 7.5% in Isfahan,[16,17] 3.2% in Tehran,[18] and 2.1% in Zanjan.[19] In a similar study conducted in Rafsanjan by Alidalaki, G6PD prevalence was 5.0%.[10] Prevalence of G6PD dehydrogenase deficiency was 25.0% in Oman,[20] and 22.0% in Nigeria;[21] despite a lower rate of prevalence of 5.0% and 3.0% in Canada and UK respectively.[22,23] Therefore, G6PD

prevalence in Sanandaj compared to other countries in the world is in the middle. In addition, due to differences in level of prevalence in different parts of Iran from one side and different countries on the other side, it could be concluded that factors such as race, geographical conditions, and weather are responsible for the differences in the number of affected cases.

Prevalence of G6PD dehydrogenase deficiency in boys and girls were 7.62% and 2.52%, respectively with a male to female ratio of 3:1. In Kazemi et al. study, female population outnumbered the disease cases.[18] In a study conducted by Khalesy et al., boys suffered from G6PD dehydrogenase deficiency 5 times more than girls.[24] In Alidalaki et al. study, there was no significant difference between boys and girls regarding the incidence of the disease.[10] In a study conducted in Mazandaran by Ahmadi and Ghazizadeh, it was reported that the incidence of the disease in boys were 3 times more than girls.[25]

Due to sex-related nature of G6PD enzyme deficiency, in different parts of Iran, especially where the disease incidence among girls and boys is the same, differences in levels of prevalence in the two sexes is likely to be related to regional and racial factors. However, it is necessary to conduct related studies further on a larger scale targeting all over Iran. Therefore, it is recommended to screen, especially cord blood of male infants right after birth. It is also recommended that further national studies on the prevalence of G6PD enzyme deficiency be conducted.

Conclusion

Prevalence of G6PD dehydrogenase deficiency was 5.00%, 7.62% in male infants and 2.52% in female in Sanandaj. Therefore, G6PD dehydrogenase deficiency is a gender related condition with a higher frequency among boys' population.

Conflict of Interests

Authors have no conflict of interests.

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