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RESEARCH ARTICLE

Assessing severity of involvement of autonomic functions in iron-deficiency anemia patients

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ABSTRACT

Background: Iron-deficiency anemia (IDA) is one of the most frequently found anemias in all countries. In India itself, 60–70% of population has IDA. Autonomic dysfunctions are common in anemias so also in IDAs. The present study was conducted to categorize these autonomic dysfunctions according to severity. **Aims and Objective:** The objective of the present study was to find if there are any autonomic dysfunctions in IDA patients and to assess the severity of autonomic dysfunction in IDA patients. **Materials and Methods:** A total of 60 patients of IDA were selected from hematology OPD and included in the study. The patients were subjected to autonomic function tests, and the results of the test were compared with age and socioeconomically matched healthy subjects. **Results:** Comparing the pattern of involvement of autonomic nervous system in IDA patients and the severity of autonomic dysfunction, it was seen that 13 (22%) had normal functions, early involvement was seen in 17 (28%) IDA patients, definite involvement is seen in 22 (37%) patients, and 5 (8%) had severe involvement, while remaining 3 (5%) had atypical involvement. **Conclusion:** Autonomic dysfunction manifests in IDA patients. This autonomic dysfunction may vary from early involvement to severe involvement. Severe autonomic dysfunction may even cause death in some cases.

KEY WORDS: Autonomic Function; Iron-deficiency Anemia; Autonomic Dysfunctions

INTRODUCTION

Iron deficiency is the most ubiquitous cause of anemia worldwide. Approximately 1.6 billion populations who are anemic suffered from iron-deficiency anemia (IDA). It is the most common cause of anemia in children and adults.[1] Problem in India is graver as 60–70% of all IDA patients live in India. Lack of food is a significant factor for IDA; therefore, it is widespread in people living in chronic poverty.[2]

IDA deteriorates the patient's health extensively. In the urban areas, with all diagnostic facilities available, IDA can be easily identified and treated. Ironically, it is a major health issue for the rural population where the diagnostic facilities are not often available.

IDA is also coupled with various symptoms such as irritability, palpitation, dizziness, breathlessness, headache and fatigue, defective structure and function of epithelial tissues, defect in immune system, impaired muscular performance, abnormalities of muscle metabolism, and developmental delay. Some literature also states that there occurs a autonomic dysfunction, thereby resulting in irregularities in temperature balance as well as the vasomotor changes in

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terms of increase in heart rate and decrease in blood pressure, arrhythmias, etc.[3,4]

The autonomic nervous system is cardinal mechanism which helps in stressful situations, and it is adversely affected in IDA patients. However, there are limited studies elaborating association of autonomic functions and IDA. It is, therefore, important to bring together more information about the status of autonomic nervous system in IDA. It is also important to know the severity of such autonomic dysfunctions as it will affect the normal functioning of most visceral organs. Severe involvement of autonomic nervous system may even cause death of the patient as it regulates some cardinal functions of the body.

The objective of the present study was to obtain more information about the status of autonomic function in IDA as well as to find the severity of autonomic dysfunctions. Assessment of autonomic function was done with the simple autonomic function tests which are non-invasive as well as gives accurate results.

Objective

The objective of this study was to find if there are any autonomic dysfunctions in IDA patients and to assess the severity of autonomic dysfunction in IDA patients.

MATERIALS AND METHODS

The study was planned on IDA patients visiting hematology clinic of a reputed medical college. The prior permission of college ethical committee was taken. A total of 60 IDA patients, visiting hematology OPD, were selected for the study and compared with 60 subjects of the same age group and same socioeconomic conditions were selected. Procedure was well explained, and informed consent was taken from the study group as well as from control group before starting the study.

For study IDA patients with Hb level <11 g%, serum iron <30 microgram/dl, total iron binding capacity >400 micrograms/dl[5] of age group 20–40. For comparison subjects with Hb level more 13 g%[2] of same age group were selected from general population.

IDA patients and controls of age <20 years and >40 years were excluded from the study. Patients having Hb level >11 g% or having diseases causing autonomic dysfunctions were excluded from the study.[6] Study group and subjects were explained the purpose and procedure of the study. Written consent was taken from both the groups. The measurement of hemoglobin level, serum iron, and serum total iron binding capacity of patients was done.

After the initial screening, autonomic function tests were carried out on IDA patients and controls. The autonomic function tests included were deep breathing test (sinus arrhythmia), valsalva test, orthostatic test, hand grip test, and cold pressor test.

The procedure starts with obtaining the basal heart rate and blood pressure. When consecutive recording of heart rate and blood pressure taken at a difference of 5 min found the same, then those recordings were considered as basal values.[7] After achieving basal heart rate and blood pressure, autonomic function tests were conducted on both the groups which are as follows.

Deep breathing test that is changes in heart rate during deep respiration. In this test, the subject was instructed to breathe slowly and deeply with a speed of 6 times in 1 min. Duration of inspiration and expiration of 5 s respectively. The subject was constantly instructed when to inhale and exhale. A continuous electrocardiography (ECG) tracing was recorded after making the individual practice twice. The heart rate variations are maximum when the test is performed in this manner, i.e., 6 breaths/min.[8]

Maximum and minimum R-R intervals during each respiratory cycle were carefully calculated with a ruler. Mean difference between maximum and minimum heart rate intervals was calculated by formula. Heart rate variation during deep breathing test = heart rate MAX during inspiration – heart rates MIN during expiration.[7] The results were interpreted as normal when heart rate variation is ≥15 beats/min. The results were said borderline or inconclusive when heart rate variation is in between 11 and 14 beats/min. Definite involvement or abnormal deep breathing test when heart rate variation is ≤10 beats/min.[7]

Orthostatic test that is heart rate and blood pressure response to instant standing. For this, ECG machine was attached to the subject. The blood pressure cuff was tied to the right arm and the sphygmomanometer was held at heart level. With this arrangement, the subject was asked to stand up from the lying down position and was instructed to stay immobile for 2 min. The ECG was recorded from about 15 beats before to about 40 beats after standing. The maximum R-R interval around 30th beat and minimum R-R interval around 15th beat were measured with a ruler. The subjects' blood pressure was recorded when lying down and when subject stands up.[9]

When normal subject is made to stand up from lying down position, there is a characteristic immediate shortening of R-R interval that is maximum around the 15th beat (tachycardia) followed by a relative increase that is maximum around the 30th beat (bradycardia), thus giving a 30:15 ratio. 30:15 ratio was calculated by formula maximum R-R interval at 30th beat divided by minimum R-R interval at 15th beat.[7]

The results were interpreted as normal when 30:15 ratio is ≥1.04 and fall in systolic blood pressure ≤10 mmHg. Results were said borderline when 30:15 ratio is in between 1.01 and 1.03 and fall in systolic BP is 11–29 mmHg. Results were

marked abnormal when 30:15 ratio is ≤1 and fall is systolic blood pressure is ≥30 mmHg.[7]

Valsalva test was performed by making subject blow air in sphygmomanometer. A subject had to hold mercury column to 40 mmHg for 10 s. Continuous measurement of heart rate was done with ECG machine during this test as well as up to 15 s after the test ends.[10] Then, valsalva ratio was calculated by formula – Maximal R-R interval (s) after end of valsalva maneuver to minimum R-R interval (s) during valsalva maneuver.[7] Results were interpreted as normal when valsalva ratio is ≥1.21. The results were interpreted as borderline or inconclusive when valsalva ratio is in between 1.11 and 1.20 and abnormal results when valsalva ratio is ≤1.10.[7]

Hand grip test – a hand grip dynamometer was used for this test. The subject was asked to press the hand grip dynamometer with maximum effort. The reading of the handgrip dynamometer was noted. Then, the subject was asked to maintain a pressure of 30% of maximum effort for 5 min. The rise in blood pressure was measured.[11] The results were interpreted as normal when a rise in diastolic blood pressure is ≥16 mmHg. The results were borderline when the rise in diastolic blood pressure is 11–15 mmHg and abnormal when rise in diastolic blood pressure is ≤10 mmHg.[7]

Cold pressor test was performed by making subject to submerge the one hand in cold water of temperature 4°C for 1 min. Blood pressure of subject was measured in the opposite arm before and after test.[12] The results were interpreted normal when diastolic blood pressure was raised >10 mmHg. If the blood pressure does not increase, it is considered as abnormal response.[7]

After performing all the above tests, test results were arranged according to the finding, i.e., normal test results, borderline test results, and abnormal test results. Then, autonomic dysfunctions were categorized as follows:[13]

Normal patients or no autonomic dysfunction	**All the autonomic function tests showed normal or one borderline results; then, person is considered as normal**
Early involvement (beginning of autonomic dysfunctions)	When one of the three heart rate tests which tests parasympathetic involvement is abnormal or two heart rate tests show borderline results considered as early involvement
Definite involvement (definite autonomic dysfunction)	When two or more of the heart rate tests show abnormal results, then there is definite involvement of autonomic nervous system
Severe involvement (autonomic dysfunction of severe strength)	Two or more heart rate tests show abnormal results and one or more blood pressure tests show abnormal or borderline results considered as severe involvement of autonomic nervous system
Atypical involvement	Any other combination of involvement of abnormal heart rate test and blood pressure test is considered as atypical involvement of autonomic nervous system

RESULTS

In the present study, when the patients and controls were tested with the autonomic function tests, it has been found that a significant number of patients showed deranged results of the tests as compared to controls. The data were compared by Pearson Chi-square test. The findings of the present study are presented in Tables 1-7.

Table 1: Deep breathing test

Heart rate variation	**Group**		**Chi-square test *P* value**	**Inference**
	Controls	**Patients**		
Abnormal test results	0	36	<0.0001	Significant
Normal test results	60	24		

Table 2: Valsalva test

Valsalva ratio	**Groups**		**Chi-square test *P* value**	**Inference**
	Controls	**Patient**		
Abnormal test results	0	24	<0.0001	Significant
Normal test results	60	36		

Table 3: Orthostatic test

30:15 ratio	**Group**		**Chi-square test *P* value**	**Inference**
	Controls	**Patient**		
Abnormal test results	0	24	<0.0001	Significant
Normal test results	60	36		

Table 4: Orthostatic test

Fall in systolic B.P.	**Group**		**Chi-square test *P* value**	**Inference**
	Controls	**Patient**		
Abnormal	0	2	0.475	Non-significant
Normal	60	58		

Table 5: Sustained hand grip test

Rise in diastolic B.P.	**Group**		**Chi-square test *P* value**	**Inference**
	Controls	**Patient**		
Abnormal	0	3	0.2422	Non-significant
Normal	60	57		

Table 6: Cold pressor test

Rise in diastolic blood pressure	Group		Chi-square test *P* value	Inference
	Controls	Patients		
Abnormal	0	3	0.2422	Non-significant
Normal	60	57		

Table 7: Percentage involvement of patients according to severity

Severity of autonomic dysfunction	*n*	%
Normal	13	22
Early involvement	17	28
Definite	22	37
Severe	05	08
Atypical	03	05
Total	60	100

DISCUSSION

The results of all tests in each patient were classified as normal or abnormal. In the study, it was found that 13 (22%) patients of IDA had normal autonomic functions and remaining 47 (78%) had one or more abnormal autonomic function tests, that is, these patients had evidence of autonomic dysfunction.

Comparing the pattern of involvement of autonomic dysfunctions in IDA patients, it was seen that 13 (22%) had normal functions, early involvement was seen in 17 (28%), definite involvement is seen in 22 (37%), and 5 (8%) had severe involvement, while remaining 3 (5%) had atypical involvement.

Autonomic dysfunction is a common feature of many anemias such as sickle cell anemia and thalassemia. Many previous studies show that the autonomic dysfunctions are also commonly involved in IDA. Nand *et al*. conducted a similar study in chronic severe anemia patients and also showed abnormal results of deep berating test, valsalva ratio, cold pressor test, and intravenous atropine test. These results are similar to findings of our study.[14] Lakhotia *et al*. performed autonomic function tests on anemics and also found that there occurs basal parasympathetic dysautonomia in anemics.[15] Yokusoglu *et al*. in their study assess the autonomic function in the IDA patients using heart rate variability. In their study, they found that there is parasympathetic withdrawal in IDA patients which leads to autonomic imbalance in IDA patients.[16] The cause for autonomic dysfunction in IDA can be hypoxia in tissues. Carotid bodies play a essential role in pressor response to hypoxemia and hypoxia in man. If the duration of hypoxia is more, the ability of carotid body to respond to hypoxic stimulus is blunted or carotid body becomes insensitive.[17]

It is very important to know the severity of autonomic dysfunction in IDA to find out the prognosis of the disease. Many previous studies state that autonomic activity essentially deranged in IDA patients,[18] but there are limited data regarding severity of autonomic dysfunctions. Therefore, it is necessary to conduct more similar studies.

CONCLUSION

In the present study, 78% of patients of IDA showed autonomic dysfunction. The autonomic nervous system regulates vital functions in the body important for day-to-day life as well as response during emergency situations. Abnormality in autonomic nervous system may cause life-threatening cardiac arrhythmias. It is, therefore, essential to acquire more information about autonomic nervous system status in IDA patients.

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