Development Of Early Diagnosis Algorithm Using Mathematical Ratio Models With Biochemical Parameters In SMA Type I Disease

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Abstract

Objective: Early diagnosis is life-saving in spinal muscular atrophy (SMA), a disease that is defined as a rare disease in the community and affects one person in ten thousand. When laboratory tests are examined from the diagnostic tests, it should be checked whether there is a homozygous deletion of the survival motor neuron 1 (SMN1) gene as the first diagnostic parameter for a patient who is thought to have spinal muscular atrophy (SMA). In order to be sure of the diagnosis, it is necessary to look at the creatine kinase (CK) value of the patient and the nerve conduction results that will be obtained from the results of electrophysiological tests such as electromyography (EMG). It was aimed to develop an early diagnosis algorithm by using a mathematical ratio model to diagnose spinal muscular atrophy disease early, by proportioning the length of the electrocardiogram (ECG) frequency with the creatine kinase value being higher than normal.

Material and Method: A group of people with SMA disease and a group of healthy people were used in the study. Serum creatine kinase values of all patients were measured and the length of the electrocardiogram (ECG) frequency was measured. These two values are proportioned.

Result and Discussion: As a result of literature studies, the frequencies of electrocardiogram tremors and creatine kinase (CK) values of healthy people were compared. Electrocardiogram (ECG) frequencies and creatine kinase values of sick people were also compared. The range value of healthy people and the range values of sick people were compared and a range of values specific to sick people was determined. Based on this range, patients with vibration frequency / creatine kinase values between 0.125-0.175 can be diagnosed. This study will contribute to the development of computer-based android applications for diagnosis for patients with spinal muscular atrophy (SMA) with codes 0 and 1, using the inference that the patient is healthy as the value approaches 1 and the value approaches 0.

Keywords: Rare diseases, Spinal muscular atrophy (SMA), Creatine kinase (CK), Electrocardiogram (ECG).

1 Introduction

Among the diseases seen in the society, diseases with a diagnosis rate of less than one in two thousand are called "rare diseases". It can be said that more than one system is generally effective in the formation of rare diseases. It is known that 80% of this is due to genetic factors and 20% to environmental factors or unknown reasons. It can be said that there have been five thousand to eight thousand rare diseases so far. A substantial portion of the patients suffering from these diseases die before the age of five.

Difficulties are experienced in the diagnosis, treatment and monitoring of the disease due to the fact that they affect a small number of people and cannot be determined. Therefore, these patients should be treated more specifically than patients suffering from other health problems seen in the community.

When patients first visit the hospital, there are difficulties such as the fact that rare diseases do not come to mind first, considering the results obtained from laboratory findings and other tests.

Getting the correct diagnosis of many patients causes a lot of time and financial loss, and sometimes it costs their lives.

Spinal muscular atrophy (SMA) disease is one of the most common rare diseases in the world and in our country. Spinal muscular atrophy occurs in recessive inheritance, that it is a single gene disease. Rare disease is encountered in one person in every ten thousand live births in the society, and the rate of being a carrier of the disease is approximately one person in 50. Spinal muscular atrophy (SMA) disease is a rare life-threatening disease that can result in muscle weakness and even paralysis, caused by the degeneration of alpha motor neurons from the large lower motor neurons directly responsible for muscle contraction in the spinal cord.

SMA type 1, also known as 'werdnig-hoffmann' disease, which is one of the subtypes of SMA disease, is the most common type that constitutes half of the SMA diagnoses.

It is known that in individuals with a type of spinal muscular atrophy disease, indicative symptoms begin individuals can not sit
without support. If these patients are not treated as soon as symptoms begin, they can not survive for more than two years. In these patients, abnormally low muscle tone occurs together with symmetrical muscle paralysis that prevents them from controlling their head. Classically, upward movements of body parts such as arms and legs are not seen and the baby’s mobility is generally less [1].

In recent years, it is known that severe spinal muscular atrophy type 1 patients generally have had a hole on the atrial septum that separates the right and left atrobes of their hearts, and research and findings on these damages on the autonomic nervous system have increased. This damage to the heart can lead to heart rhythm disturbances or even sudden death of the patient. When laboratory tests of spinal muscular atrophy type 1 disease are examined, it should be checked whether there is a homoyzogous deletion of the survival motor neuron 1 (SMN1) gene as the first diagnostic parameter for a patient who is thought to have SMA. The factor that proves the diagnosis of SMA is the absence of SMN1 exon 7 (with or without deletion of exon 8). This examination gives almost 100% correct results. If it does not allow accurate diagnosis, even in a small part, and the test result is negative, it is necessary to look at the patient’s creatine kinase value and the nerve conduction results that will come out of the results by performing electro-physiological tests such as electromyography (EMG). Genetic tests are now used in multiplex polymerase chain reaction method, which enables the detection of mutations in the number of deoxyribo nucleic acid (DNA) and ribo nucleic acid (RNA) in genes whose abbreviation is ‘MLPA’, known as multi-ligation-dependent probe amplification, and also provides safe results [2].

SMA Type 1 patients must be subjected to additional diagnostic tests in order to get the most accurate result after the gene test. Electrophysiological examinations are at the top of these tests, and if these tests show that the patient is not an SMA patient, other tests should be performed. Another test required to make this diagnosis correct is to examine the serum creatine kinase value of the patient. In general, creatine kinase value is slightly increased in patients with spinal muscular atrophy.

2 Material and method

In this study, early diagnosis parameters of SMA disease with ECG tremors and elevated creatine kinase has been examined. Then, the relationship between early diagnosis parameters has been examined by mathematical modeling.

2.1 Relationship Between Serum Creatine Kinase (CK) Values with SMA Disease

Creatine kinase (CK), also known as phosphocreatine kinase and which is a kind of enzyme, causes the formation of energy-generating mechanisms in our body. It works mostly in the heart, muscles in the body and cells in the brain. The creatin kinase (CK) level in human blood depends on many factors. However, the muscular standard creatine kinase value has an average of 22 to 198 units in 1 litter of blood serum. This level can rise up to two hundred thousand per litter in some health conditions [3]. Biochemical research in patients with childhood spinal muscular atrophy (SMA) is important to rule out known metabolic defects or primary dystrophic processes of the muscle. Many studies of SMA have reported increased serum creatine kinase activities at a variable rate [4].

2.2 SMA Patients and Electrocardiogram Relationship

In the past, it has been reported that tremors recorded on the electrocardiogram may be a common finding of SMA, despite some inconsistencies. The tremors of the isoelectric line on routine electrocardiograms have been described in patients with spinal muscular atrophy and interpreted as fasciculations of the denervated muscles. To evaluate this phenomenon, 13 patients with spinal muscular atrophy were studied (average age: thirty-seven months).

To fully describe the features of the spikes, all electrocardiograms were reported while patients were in the optimal thermal, environmental, and psychological state. Mild sedation was provided with oral benzodiazepines in three children. During electrocardiogram recording, none of the patients had clinically significant limb muscle tremor.

The first electrocardiogram was recorded routinely; A second track was then recorded with double sensitivity and double velocity. In addition, all patients were evaluated clinically and M-mode and cross-sectional echocardiography was performed. Regular and continuous increases in the isoelectric electrocardiographic line were recorded in 12 patients (93.4%); frequencies varied between 39-48 cycles/set (Mean: 42.08, F: 2.64). An ‘abnormal’ electrocardiogram was found in all patients with severe spinal muscular atrophy [2].

We conclude that the continuous tremor in the isoelectric line of the electrocardiogram represents a feature of spinal muscular atrophy in these patients. These changes in the electrocardiogram are a result of muscle fasciculations and do not mean that the heart has any abnormalities.

In patients with spinal muscular atrophy, routine electrocardiograms revealed constant abnormalities in the isoelectric line in almost all cases [2].

2.3 The Ratio Consisting of Early Diagnosis Parameters of SMA Disease

In a study conducted, an increased serum CK activity (762 U/L; normal: 25-170) was accidentally recorded at the age of 32 in a 33-year-old male patient without a family history of SMA, and he went to control at the age of 33 due to the high level of creatine kinase.

The patient, whose other neurological tests and muscle difficulty and muscle reflex tests of the patient were normal, was diagnosed with SMA. In addition, an abnormality was observed in the patient’s ECG. As a result of this research, the importance of serum creatine kinase value has been emphasized [5].

In another study, the biochemical values of 4 patients with spinal muscular atrophy, including a baby, identical twins, and a twelve-year-old girl were examined. In the test, where the normal value was accepted as 150 U / L, the CK value of the baby was 580 U / L, the value of the 1st twin was 390 U / L, the value of the 2nd twin was 260 U / L and the value of the 12-year-old girl was 520 U / L.

Considering these results, it was seen that there was no significant relationship between age and creatine kinase values. As a result of this study, it was observed that the serum creatine kinase values in the blood of the patient with spinal muscular atrophy disease increased, as in other studies [6].

As a result of these studies, when looking in terms of serum creatine kinase level, it is seen that the creatine kinase value in the serum of sick people is at least 2 times the serum creatine kinase value of healthy people.

In 12 of 13 patients (93.4 %) with spinal muscular atrophy, various degrees of abnormalities were already evident on the first routine electrocardiogram. The scars showed sharp tremors of fairly regular duration and frequency, consistent with the potentials due to muscle fasciculation. The spikes always had higher amplitude at the limb ends compared to the nipples, and showed no difference between standard and raised tips. These were always less than 40 milliseconds.

In two patients, spikes were present only in the limb leads. One patient had a normal electrocardiogram. She was a 14-year-old girl with mild muscle atrophy and minimal weakness. When the scan of different spinal muscular atrophy forms were compared, the...
most prominent abnormalities were seen in intermediate forms, mild and severe forms. Spikes were always less than 0.1 mV in amplitude [7]. In the light of the studies carried out, vibration frequencies and serum creatine kinase values in the electrocardiogram were compared and a range of values was determined. While finding this value range, the frequency of healthy people on the average electrocardiogram graph and the average creatine kinase values of healthy people; A result was obtained by comparing the frequencies and creatine kinase values in the average electrocardiograms of people with SMA (Figure 1).

<table>
<thead>
<tr>
<th>T-P Interval on ECG Graph: Vibration in 1 second: frequency</th>
<th>Healthy People</th>
<th>People with SMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Frequency: 3.125 cycle/sec</td>
<td>Average: 42.08 cycle/sec</td>
<td></td>
</tr>
<tr>
<td>Average CK Range: 25-170</td>
<td>Average CK Range: 240-670</td>
<td></td>
</tr>
<tr>
<td>3.125 3.125</td>
<td>42.08 42.08</td>
<td></td>
</tr>
<tr>
<td>25 170</td>
<td>240 670</td>
<td></td>
</tr>
<tr>
<td>(0.125, 0.018)</td>
<td>(0.175, 0.062)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. The Ratio Consisting of Early Diagnosis Parameters of SMA Disease.

It is seen in the analyzed healthy and sick individuals that when compared with the average ECG frequency values of healthy people by taking the creatine kinase values of 25-170 for a healthy person by taking the approximate lower and upper limits, it was examined that healthy people included a certain range ratio. On the other hand, a certain range was determined by comparing the mean ECG frequency values of the diseased individuals with the average upper and lower limits of the high CK values obtained from the sick individuals, and when these two early diagnosis parameters were compared for spinal muscular atrophy disease, it can be said that people with the range of 0.125-0.175 are sick (Fig.1).

3 Result and Discussion

Spinal muscular atrophy, which is the most common disease among these rare diseases in our country, is an autosomal recessive neurodegenerative disease characterized by degeneration of spinal motor neurons, skeletal muscle atrophy, muscle hypotonia and severe weakness [4]. The leading diagnostic parameter of this disease is gene testing of patients suffering from SMA. However, the gene test rarely gives the correct result. Tests performed in addition to gene testing are vital for early diagnosis of patients. The most accurate parameter among these tests is to analyse the patient’s serum creatine kinase values. It is known that creatine kinase values in serum are among the most sensitive and diagnostic tests in determining muscle damage and it is mostly the first test used in suspected muscle disease cases.

However, as serum creatine kinase can be assessed by different methods and may vary in different ethnic groups and during pregnancy. For this reason, each laboratory should establish its own normal serum creatine kinase activities. CK serum levels are usually normal or only slightly elevated in SMA.

In another examination, it was reported that, despite some inconsistencies in the studies, tremors recorded in the electrocardiogram may be a common finding of SMA. The tremors of the isoelectric line in routine electrocardiograms have been described in patients with spinal muscular atrophy and interpreted as fasciculation’s of damaged muscles.

As a result of literature studies, the frequencies of electrocardiogram tremors and creatine kinase values were compared in healthy people. ECG frequencies and creatine kinase values of sick people were also compared.

The range values of healthy people and sick people were compared and a range of values specific to sick people was determined. Based on this range, patients with vibration frequency/ creatine kinase values between 0.125-0.175 can be diagnosed.

It is a study that will contribute to the development of computer-based android applications for diagnosis for patients with SMA with codes 0 and 1, using the inference that the patient is closer to 1, and the people are healthy as the value approaches 0.

4 Conclusion

As a result of this review, it appears that patients with spinal muscular atrophy have increased possibilities for early diagnosis. A new diagnostic parameter was created by comparing the increase in creatine kinase value, which is one of the other diagnostic parameter, ECG tremors. This value between 0.125-0.175, which is found by comparing the creatine kinase values of the patients with the ECG frequency, is said to be close to 0 if the patients are healthy, and 1 if the patients are ill. For SMA patients in the future, this value range will be converted to 0 and 1 codes and can be used with smart devices as an application.

Abbreviations

CK: Creatine Kinase  
DNA: Deoxyribo Nucleic Acid  
ECG: Electrocardiogram  
EMG: Electromyography  
MLPA: Multi-Ligation-Dependent Probe Amplification  
mV: Milli Volt  
SMA: Spinal Muscular Atrophy  
SMN1: Survival Motor Neuron 1  
U/L: Unit / Liter

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Ethical issue

Authors are aware of, and comply with, best practice in publication ethics specifically with regard to authorship (avoidance of guest authorship), dual submission, and manipulation of figures, competing interests and compliance with policies on research ethics. Authors adhere to publication requirements that submitted work is original and has not been published elsewhere in any language.

Competing interests

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.
Authors’ contribution

All authors of this study have a complete contribution for data collection, data analyses and manuscript writing.

References