ISSN 2231-346X (Print)
JUSPS-A Vol. 29(2), 66-70 (2017). Periodicity-Monthly
Section A
(Online) ISSN 2319-8044

JOURNAL OF ULTRA SCIENTIST OF PHYSICAL SCIENCES
An International Open Free Access Peer Reviewed Research Journal of Mathematics
website:- www.ultrascientist.org
Estd. 1989

Mathematical modeling of Friedreich's ataxia – a genetic neuro-muscular degenerative condition

SWASTI WAGH[1] and D.K. WAGH[2]

[1]M.Sc. Applied Mathematics from G.S. Institute of Tech. and Sc., Indore, M.P., India
[2]Ph.D., Retired Prof. of Mathematics from G.S. Institute of Tech. and Sc. ,Indore, M.P., India
Corresponding Author Swasti Wagh :Email; swastiwagh@gmail.com
http://dx.doi.org/10.22147/jusps-A/290203

Acceptance Date 18th Dec., 2016, Online Publication Date 2nd Feb., 2017

Abstract

In this paper we propose a mathematical model of Friedreich's Ataxia (FA) – a genetic neuro-muscular degenerative condition which causes imbalance, in-coordination and jerky limb movements. These continue to increase till patient loses independence and becomes wheelchair bound. Currently Friedreich's Ataxia (FA) is not considered an important health problem because of its relatively low prevalence in the general population. However with improvement in health care diagnosis and delivery provisions, more and more people with Friedreich's Ataxia (FA) are being diagnosed and surviving. This means that its incidence and prevalence is bound to change. We have used a mathematical model to estimate generational increase in the number of patients and carriers with FA. The results portray a scary picture and hence demand measures to take it more seriously by health care providers.

Key words : Friedreich's Ataxia, Stochastic matrix, Probability vector, Fixed point.

1 Introduction

Friedreich's Ataxia (F.A.) is a neuro-muscular degenerative condition[1,2]. It is characterized by gradually progressive deterioration in balance, muscle coordination and jerky limb movements leading to loss of independence. It is also associated with slurred speech, diabetes, vision, hearing and cardiac problems. So far, there has been little headway in finding a cure or measures to slow the progression. It is now well established that it is a hereditary disorder and transmitted in autosomal recessive fashion. The Friedreich's Ataxia (FA) is unique to other autosomal recessively transmitted hereditary disorders in having adult onset and long and protracted course leading to much larger impact on overall prevalence with relatively low incidence. This unique nature of FA led to wonder whether we could develop a mathematical model of Friedreich's Ataxia (FA) using mathematics of genetics. The model developed as a result reveals a startling and scary picture and demands Friedreich's Ataxia (FA) to be taken more seriously to put resources in finding medical and non-medical measures to deal with a potential non-infectious epidemic aka obesity.

2. Genetics of Friedreich's ataxia :

According to U.S. National Library of Medicine's Genetics Home Reference, Friedreich's ataxia is a genetic defect that's inherited from both parents by what is called "autosomal recessive transmission." The disease is linked to a

gene called FXN. Normally this gene will cause body to produce up to 33 copies of a specific DNA sequence. In people with Friedreich's ataxia, this sequence may repeat 66 to over 1,000 times. As per the principles of autosomal recessive inheritance, an individual can develop Friedreich's Ataxia (FA) if he/she inherits both the copies of abnormal gene whereas if he/she inherits only one copy of abnormal frataxin gene then the individual is a Friedreich's Ataxia (FA) carrier. If we denote normal FXN gene by 'F' and the abnormal gene (non functioning gene) by 'f ' then individuals with genotype–

1. (f,f) suffer from Friedreich's Ataxia (FA)
2. (f,F) or (F,f) are carriers of Friedreich's Ataxia (FA)
3. (F,F) are normal

The diagrams (1), (2) and (3) explain the possible genotypes of offspring when a carrier (F,f) is crossed with patient(f,f), a carrier is crossed with carrier and a carrier is crossed with a normal.

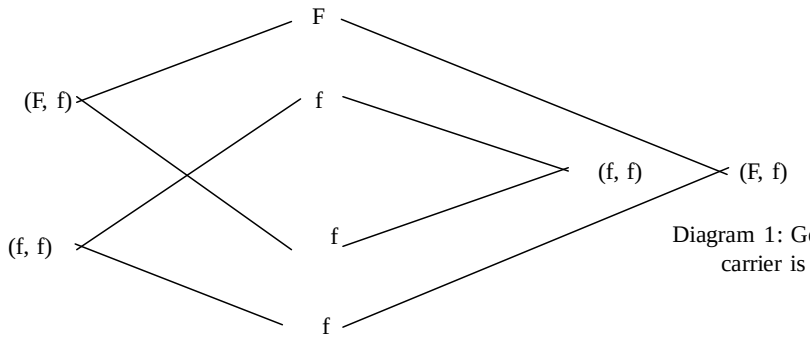

Diagram 1: Genotypes of offspring when carrier is crossed with a patient

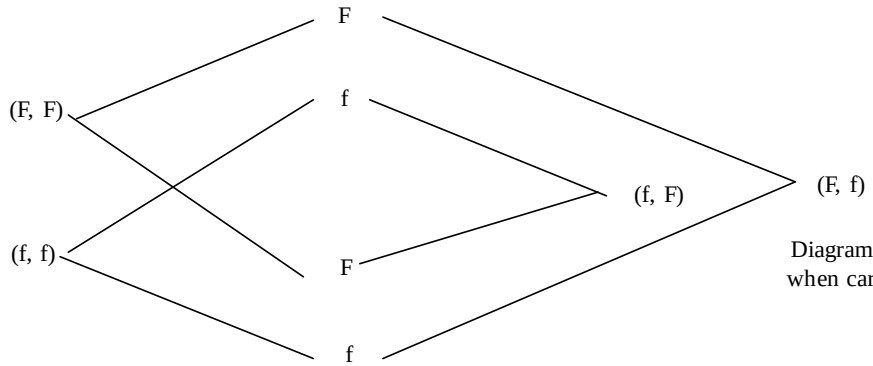

Diagram 2 : Genotypes of offspring when carrier is crossed with a carrier

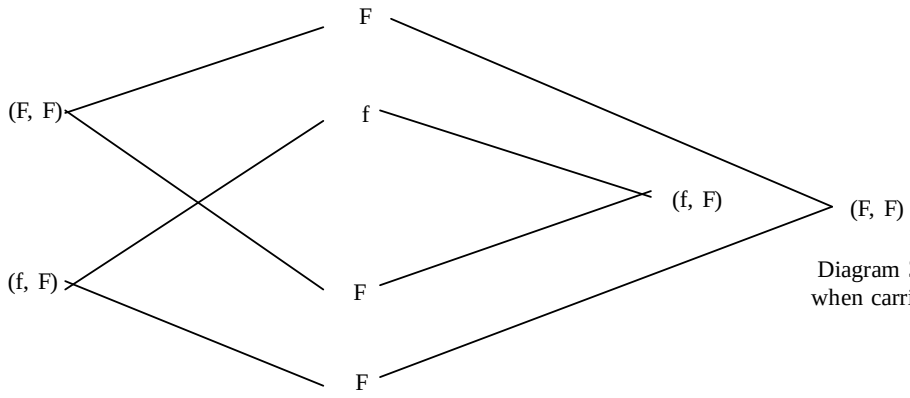

Diagram 3 : Genotypes of offspring when carrier is crossed with a normal

Similarly, we can draw diagrams for patient and normal crossing with the population. These diagrams can be used to calculate the probabilities of offspring being patient, carrier and normal.

3. Mathematics of genetics :

Calculating the probabilities of offspring being patient, carrier, normal, when a patient, carrier, normal is crossed with an individual in the population, we get following fundamental genetic matrices-

$$A = \begin{pmatrix} 1 & 0 & 0 \\ 0.5 & 0.5 & 0 \\ 0 & 1 & 0 \end{pmatrix} \quad (3.1)$$

$$B = \begin{pmatrix} 0.5 & 0.5 & 0 \\ 0.25 & 0.5 & 0.25 \\ 0 & 0.5 & 0.5 \end{pmatrix} \quad (3.2)$$

$$C = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0.5 & 0.5 \\ 0 & 0 & 1 \end{pmatrix} \quad (3.3)$$

These are stochastic matrices. The matrix A gives the probabilities of offspring being patient, carrier or normal when a patient is crossed with an individual in the population. Similarly the matrices B and C give the probabilities of offspring being patient, carrier and normal when a carrier and a normal are crossed with an individual in the population.

4. Mathematical modeling of Friedreich's ataxia :

As stated in section 2 "Genetics of Friedreich's Ataxia''; the offspring of genotype (f,f) is a patient of F.A, offspring of genotype (F,f) or (f,F) is a carrier of F.A. while the offspring of genotype (F,F) is a normal child.

We consider the case when a carrier of F.A.crosses with an individual in the population. This case is very important because the carrier does not know that he can produce F.A. patient offspring. The case of F.A. patient crossing with the population we omit on the assumption that patient is wise enough and does not take the risk of producing offspring on the basis of his own condition. Third case of normal crossing with the population is not considered because as seen from the matrix C it does not produce F.A. patient.

We suppose that the probability vector of the initial population is

$$\mathbf{P_0} = (p_0 , q_0 , r_0) \quad (4.1)$$

Where the components p_0 , q_0 , r_0 of the vector $\mathbf{P_0}$ are the probabilities that an individual of the population is F.A. patient, F.A. carrier or normal respectively.

The crossing of a carrier with an individual in the population is governed by matrix B. The product $\mathbf{P_0}B$ gives the probability vector of the population of next generation. We shall denote it by $\mathbf{P_1}$ and call it the probability vector of first generation. Thus

$$\mathbf{P_1} = \mathbf{P_0}B = (p_1 , q_1 , r_1) \quad (4.2)$$

Its components p_1 , q_1 , r_1 denote the probabilities that an individual of population is F.A. patient, F.A. carrier or normal respectively. Similarly the probability vectors of second, third and higher generations are given by –

$$\mathbf{P_2} = \mathbf{P_1}B = \mathbf{P_0}B^2 = (p_2 , q_2 , r_2) \quad (4.3)$$

$$\mathbf{P_3} = \mathbf{P_2}B = \mathbf{P_0}B^3 = (p_3 , q_3 , r_3) \quad (4.4)$$

… … …

$$\mathbf{P_n} = \mathbf{P_{n-1}}B = \mathbf{P_0}B^n = (p_n , q_n , r_n) \quad (4.n)$$

The number of patient, carrier and normal in a generation can be found by multiplying the components of probability vector of the generation by the total number of individuals in the population.

5. Mathematical calculations :

Since F.A. is a rare disease, we suppose that in the initial population of one Lac there is no patient, only two carriers and others are normal. Thus the initial probability vector of the population is,

$\mathbf{P_0}$ = (0 , 0.00002 , 0.99998) (5.1)

Putting for the matrix B from eq. (3.2) and for $\mathbf{P_0}$ from eq. (5.1) in the eqs. (4.2), (4.3), (4.4)……. We get the probability vectors of 1st, 2nd, 3rd, ……. Generation. These are,

$\mathbf{P_1}$= (0.000005 , 0.5 , 0.4999949)
$\mathbf{P_2}$= (0.1250025 , 0.5 , 0.3749975)
$\mathbf{P_3}$= (0.1875012 , 0.5 , 0.3124987)
$\mathbf{P_4}$= (0.2187506 , 0.5 ,0.2812493)
$\mathbf{P_5}$= (0.2343753 . 0.5 ,0.2656246)
$\mathbf{P_6}$ = (0.2421876 , 0.5 , 0.2578123)
$\mathbf{P_7}$= (0.2460938 , 0.5 , 0.2539061)
……
$\mathbf{P_{25}}$ = (0.2499990 , 0.5 , 0.2500009)
$\mathbf{P_{26}}$ = (0.25 , 0.5 , 0.25)

If we multiply the components of these probability vectors by 100, we get the vectors $\mathbf{v_1}$, $\mathbf{v_2}$,$\mathbf{v_3}$,….. whose components give the percentage of patient, carrier and normals in the generation. The vectors $\mathbf{v_1}$, $\mathbf{v_2}$,$\mathbf{v_3}$,….. so obtained are–

$\mathbf{v_1}$= (0 , 50.00 , 49.99)
$\mathbf{v_2}$= (12.50 , 50.00 , 37.49)
$\mathbf{v_3}$= (18.75 , 50.00 , 31.24)
$\mathbf{v_4}$= (21.87 , 50.00 , 28.12)
$\mathbf{v_5}$= (23.43 , 50.00 , 26.56)
$\mathbf{v_6}$=(24.21 , 50.00 , 25.78)
$\mathbf{v_7}$= (24.60 , 50.00 , 25.39)
…..……
$\mathbf{v_{25}}$ = (24.99 , 50.00 , 25.00)
$\mathbf{v_{26}}$= (25.00 , 50.00 , 25.00)

6 Results and Discussion

The matrix B is a regular stochastic matrix[2] and its fixed point is (0.25 , 0.5 , 0.25) hence some power of B (as per calculation it is 26th) will become,

$$B^{26} = \begin{pmatrix} 0.25 & 0.5 & 0.25 \\ 0.25 & 0.5 & 0.25 \\ 0.25 & 0.5 & 0.25 \end{pmatrix}$$

And there after all powers of B will give the same result as B^{26}. So the probability vector of the generation ≥ 26 is

$$\mathbf{P_{\geq 26}} = \mathbf{P_0}B^{26} = (p_0 , q_0 , r_0) \begin{pmatrix} 0.25 & 0.5 & 0.25 \\ 0.25 & 0.5 & 0.25 \\ 0.25 & 0.5 & 0.25 \end{pmatrix}$$

= (0.25 , 0.5 , 0.25)

So whatever be the initial probability vector of the population, the probability vector of 26th and higher generation is

$\mathbf{P_{\geq 26}}$= (0.25 , 0.5 , 0.25)

Multiplying this by 100, we get

$\mathbf{v_{\geq 26}}$= (25 , 50 , 25)

This shows that the initial population reaches to a stable state in 26th generation in which 1/4th of the population is F.A. patient, 1/2 is F.A. carrier and remaining 1/4th is normal.

The careful study of vectors $\mathbf{v_1}$, $\mathbf{v_2}$,$\mathbf{v_3}$,….. $\mathbf{v_{26}}$ indicate that the situation is still more serious. From the table we see that it is the seventh generation in which the number of patients is almost 1/4th of the population. In first seven generations the increase in number of patient is very rapid. Generation to generation percentage increase in the number of patients in first seven generations is as under –

In the first generation there is no change in the number of patients
In the second generation increase in the number of patients is from 0 to 12.5 %
In the third generation increase in the number of patients is from 12.5 to 18.7 %
In the fourth generation increase in the number of patients is from 18.7 to 21.8 %
In the fifth generation increase in the number of patients is from 21.8 to 23.4%
In the sixth generation increase in the number of patients is from 23.4 to 24.2 %
In the seventh generation increase in the number of patients is from 24.2 to 24.6 %

The number of carriers increase to one half of the population only in the first generation and there after it remains constant.

Generation to generation percentage decrease in number of normal's in the first seven generations is as under –

In 1^{st} generation decrease in number of normal is from 99.9 to 49.9 %
In 2^{nd} generation decrease in number of normal is from 49.9 to37.4 %
In 3^{rd} generation decrease in number of normal is from 37.4 to 31.2 %
In 4^{th} generation decrease in number of normal is from 31.2 to 28.1%
In 5^{th} generation decrease in number of normal is from 28.1 to 26.5 %
In 6^{th} generation decrease in number of normal is from 26.5 to 25.7 %
In 7^{th} generation decrease in number of normal is from 25.7 to 25.3 %

7. Concluding remarks

Today Friedreich's Ataxia is considered to be a rare disease. Being genetic it passes on in offspring. Calculations based on the Mathematical Model reveal that practically in the seventh generation almost $1/4^{th}$ of the population becomes patient. This is very serious and to avoid this measures must be taken. On the basis of Mathematical Model we can suggest following measures. It follows from matrix B that if a carrier is crossed with the normal, the probability of offspring being patient is zero. Hence if the carrier is not allowed to cross with patient or the carrier the increase in population of patients can be controlled.

Acknowledgment

We express our sincere thanks to Rashmi Gupta for helping me in computer calculations and Dr. Anupam Gupta for language correction.

References

1. Kapur J.N., Mathematical Models in Biology and Medicine, Affiliated East-Wast Press Pvt. Ltd. (1985).
2. Paria G., D. Phil., D.Sc., Statistics and Stochastic Process, Scholar Publisher.