ORIGINAL ARTICLES

MENDELIAN INHERITANCE OF PROPRANOLOL RESPONSIVE HYPERTENSION IN AN EXTENDED GHANAIAN FAMILY

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SUMMARY

Two clear groups, namely hypertensives and normotensives were identified when several members of 3 generations of an extended Ghanaian family were investigated clinically and historically. Two sets, and large numbers of offspring from polygamous marriages in the family facilitated Mendelian genetic analysis. The first marriage of the female hypertensive propositus to a normotensive produced two sons; one was hypertensive the other not. Her second marriage to a hypertensive produced six offspring all hypertensive. The hypertensive son from the propositus's first marriage married two normotensive women; the first had six normotensive while the second had one hypertensive and two normotensive offspring. Two of the female offspring of the propositus's second marriage married normotensive men and had several offspring half of whom were hypertensive. This pedigree pattern could be explained on Mendelian genetic theory by postulating a pair of alleles, name (H) and (N) genes. On this hypothesis the genotype of hypertension is HH, while that of normotension is NH or NN. This makes H a recessive gene. The marriage between hypertensives (HH) and heterozygous carriers (NH) resulted in hypertensive offspring, giving the false impression that the hypertensive gene was dominant. At 30 years of age, hypertensive genotypes developed measurable high blood pressure which was consistently reducible with the B-blocker anti-renin propranolol. An abnormality in the renin-angiotensin system was postulated as the probable biochemical basis of this inherited hypertension.

INTRODUCTION

Although clinicians are aware that essential hypertension is inherited, there is no agreement on the exact mode of inheritance. In 1947 Platt[1] hypothesized that essential hypertension was a disorder transmitted by a single pair of genes with features of Mendelian dominance. Mendelian inheritance implies that those who had inherited the particular gene differed from those who had not by having some specific biochemical 'fault' or trait. Platt could neither identify the biochemical defect associated with the gene nor demonstrate the characteristics of dominant Mendelian inheritance. Meanwhile Hamilton[2,3] concluded after a series of epidemiological and statistical studies that heredity played only a small part in the aetiology of

essential hypertension and that the cause of the disease was predominantly environmental. In 1955, another school of thought led by Pickering[4] categorically stated that inheritance of hypertension was not Mendelian but plurigenic. This theory which remained entrenched for many years implied that in a population, blood pressure distribution was in a continuous variation with those at the top end labelled as hypertensive. Ostfeld and Paul[5] shared the views of Pickering et al.

In 1959 Morrison and Morris[6] after extensive clinical studies concluded that hypertension was inherited as a simple Mendelian dominant trait. Platt in 1959[7] and 1961[8] again reported that hypertension was inherited as a simple Mendelian trait. In 1963 Platt reported his findings after clinical studies of severe hypertension in 3 pairs of identical twins and 4 pairs of dizygotic twins. He concluded that the pattern he obtained could be explained by the action of a pair of genes with incomplete dominance and a frequency of 0.24 which in the homozygous gave rise to severe hypertension and in the heterozygous form to moderate elevation of blood pressure. Platt predicted that further clarification of his simple Mendelian theory could be obtained if two conditions were satisfied; firstly a long term study spanning over 20 years involving siblings and children of hypertensives, and secondly a more sensitive test than measurement of blood pressure for detection of essential hypertension. In the work reported here, the first condition was satisfied fully and the second partially or indirectly.

The purpose of this communication is to report the findings of a 20-year study on 3 generations of an extended Ghanaian family of hypertensives and normotensives. Three factors in this family namely, polygamy, large numbers of children and consistent response of their hypertension to B-blockers facilitated the application of Mendelian principles and speculation as regards an enzymic defect responsible for this familial hypertension.

MATERIAL AND METHODS

This study involved hypertensives and normotensives belonging to three generations of an extended Ghanaian family in which polygamy and polyandry resulting in half sibships occurred. A clinical investigation of the younger members of the second generation who had presented with hypertension and its complications was undertaken. Detailed family history from the above patients revealed the causes and/or mode of death and the health status of members of the first generation and older members of the second generation who were never actually looked after by the author. The investigation was then extended into the third generation, by doing routine periodic medical examination on them. Other members of the third generation have started developing hypertension and its complications and the results are included. The blood pressure was measured thrice with the patient recumbent at 10 minutes intervals, followed by once with the patient sitting and once standing. Hypertension was considered present on this first visit only if all the figures obtained were above 140 systolic and 90 diastolic. The fifth phase when sound disappeared was taken as the diastolic. Patients were then seen at monthly intervals for short interviews followed by measurement of the blood pressure. History of Bilharzia was excluded as was proteinuria with evidence of renal hypertension. Chest X-rays, ECGs, blood urea and electrolytes were done only on those who had presented with complications such as strokes, congestive cardiac failure or renal failure. In the majority the only recorded abnormality was the high blood pressure.

Treatment at the onset of the investigation was haphazard with a variety of drugs such as serpasil, aldomet and diuretics singly or in various combinations. Later it was standardized. The stardard regime consisted of propranolol 40 to 80 mg 12-hourly. The effect of treatment with propranolol was assessed after three months therapy.

RESULTS

The genealogical tree showing the hypertensives and normotensives is illustrated by Fig. 1 entitled 'Hypertensive Phenotypes in Three Generations'. Fig.2 'Hypertensive Genotypes in Three Generations' was constructed by applying the Mendelian theory of genetics to the genealogical tree shown in Fig. 1. Table 1 summarises some of the clinical features of the hypertensives shown in Fig. 1. At the the onset of this study, III^{8}, III^{14}, III^{16}, III^{18} and III^{20} were listed as normotensive with other siblings and cousins, however, each of them became overtly hypertensive soon after reaching the age of 30. Table 1 also contains information about the older members of this family who died of hypertension and its complications.

THE FAMILY TREE

The originator of this family tree was a hypertensive woman who died at the age of 62 from acute pulmonary oedema due to myocardial infarction superimposed on hypertensive heart disease. During her life-time she married twice : her first marriage, to a normotensive, produced two sons who

FIG. 1: HYPERTENSIVE PHENOTYPES IN 3 GENERATIONS

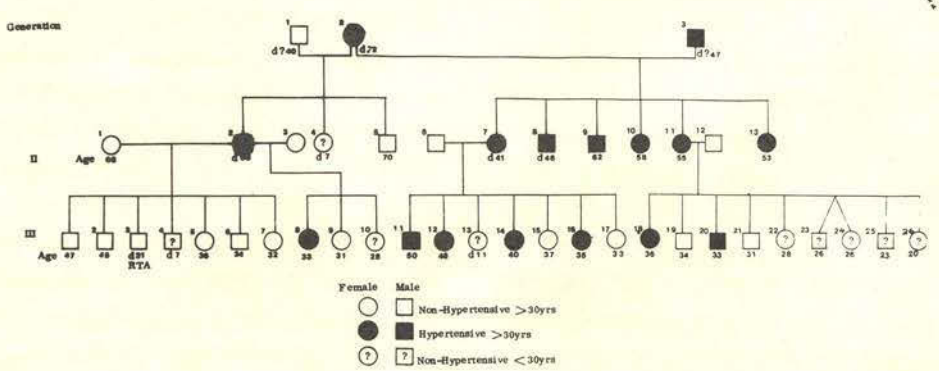
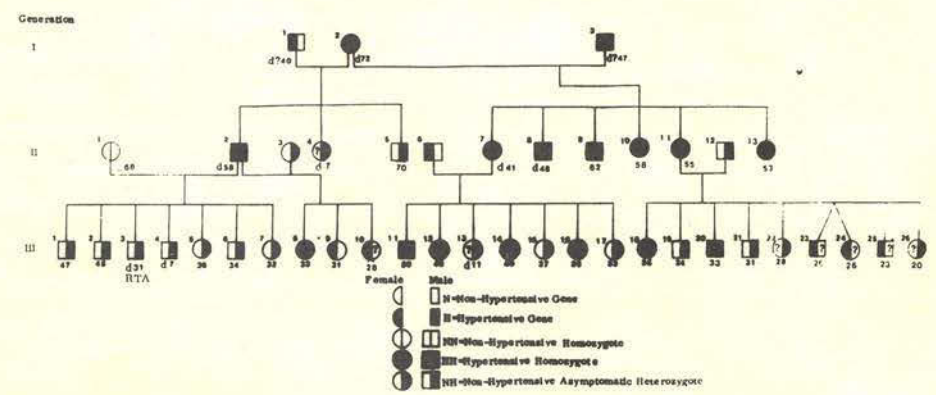


FIG. 2: HYPERTENSIVE GENOTYPES IN 3 GENERATIONS



reached adult life; one son developed hypertension (and died of a stroke at 58), the other son is not hypertensive. The second marriage of the above woman was to a hypertensive (he died suddenly at 47 from a stroke); that union produced 6 offspring who all developed hypertension on reaching adulthood. The hypertensive son from the first marriage above also married twice, each time to a normotensive. His first marriage resulted in 7 offspring of whom 6 have reached adulthood and none has developed hypertension. In contrast his second marriage also to a normotensive resulted in 3 children, one of whom is under 30; of the 2 who are over 30, only one is hypertensive. The study also included the offspring of two of the six hypertensive children of the second marriage of the propositus; the two, both women, married normotensives, and of their children who are now over 30 approximately half are hypertensive and half not.

HYPERTENSIVE PATIENTS (see Fig.1)	Sex	Age at onset	Present Age	Presenting Symptoms	Mean Blood Pressure at onset	Complications	Mean BP after 3 months propranolol	Deaths	
								Age at death	Cause of death
I_2	F	NO CLINICAL RECORDS: NOT EXAMINED BY AUTHOR						72	Left Ventricular Failure
I_3	M							?40+	Stroke (Intracranial haemorrhage (ICH))
II_2	M							58	Stroke (ICH)
II_7	F							41	Stroke (ICH)
II_8	M							48	Renal Failure
II_9	M	30	62	Stroke (ICH)	220/130	Stroke, CCF	145/95		
II_{10}	F	46	58	Headaches, obesity	190/120	Stroke, CCF	140/90		
II_{11}	F	42	55	Headache, insomnia, repeated abortions	230/140	CCF: Stillbirth	150/95		
II_{13}	F	43	53	Headaches	180/110	Nil	130/85		
III_8	F	30	33	Routine check-up, no symptoms	150/100	Nil	120/80		
III_{11}	M	41	50	Routine check-up at hypertensive survey	200/115	Stroke	140/90		
III_{12}	F	40	48	Headaches, insomnia	190/110	Nil	125/85		
III_{14}	F	35	40	Headaches, menorrhagia	170/105	Nil	120/80		
III_{16}	F	30	36	Routine check-up	165/100	Nil	120/80		
III_{18}	F	36	36	Headaches	180/110	CCF	130/90		
III_{20}	M	30	33	Routine check-up	160/95	Nil	120/75		

The above hypertensive and non-hypertensive phenotype pattern shown graphically in Fig.1, could be explained on Mendelian genetic theory by postulating the existence of a pair of alleles namely a hypertensive gene (H) and a normotensive gene (N). On the above hypothesis, the hypertensive phenotype must be homozygous for the hypertensive gene i.e. HH, whereas normotensive phenotypes could either be heterozygous NH, or homozygous for the normotensive gene NN (Fig.2). Thus this hypertensive gene is a Mendelian recessive, but its high prevalence leading to frequent marriages between the homozygous sufferers and heterozygous carriers resulted in a pedigree pattern which resembled that of a dominant trait.

The inherited tendency manifested as measurable high blood pressure only after the age of 30 equally in both men and women. The commonest complication has been stroke due to intra-cerebral haemorrhage, which has occurred in five members, three of whom died following the stroke while two survived. There has been no deaths since the onset of this study which was always combined with anti-hypertensive therapy. Initially diuretics alone or in combination with either serpasil or aldomet were used. The diuretics caused dehydration without reducing blood pressure, serpasil produced severe depression, and aldomet caused dangerous attacks of postural hypotension necessitating stoppages of treatment. When response to the above regime proved unsatisfactory as regards relieving symptoms or preventing complications, a new regime had to be introduced. The B-blocker propranolol was chosen. Starting from a low dosage of 40mg a day, an optimum dose of 80mg 12-hourly which reduced the blood pressure from 240/120 to a stabilized 160/95 in three months, was found in the first of these patients treated with propranolol. Subsequently all the hypertensives in this family were similarly treated with exactly the same results; - a smooth reduction of blood pressure accompanied by tolerable bradycardia.

DISCUSSION

Polygamy resulting in two sets of children demonstrated the segregation of homologous genes compatible with Mendelian theory. The large number of children from the marriages caused the appearance of phenotype ratios which fitted Mendelian principles. Application of classical Mendelian genetic theory to the results (Figs. 1 and 2) revealed that hypertension in this family was inherited as an autosomal recessive.

The positive family histories for hypertension with a recessive gene is due to the high frequency of the H gene and the resultant frequent marriages between hypertensives and normotensives who were heterozygous H gene carriers (NH). Genotypes HH, HN and NN were all normotensive when aged under 30. After 30 the HH genotype became hypertensive and could be distinguished from the heterozygote HN and homozygote NN by the sphygmomanometer. In order to distinguish between phenotypes corresponding to genotypes HN and NN, and to identify genotype HH, aged under 30 years, other measurable parameters (biochemical, pharmacological or physical) must be found. Consistent favourable response to B-blockers in this familial hypertension is suggestive that their hypertension is renin-dependent because propranolol, a B-adrenergic blocker, is known to reduce renin secretion.[10] This hypothesis is supported by the fact that patients with renin-dependant hypertension have been found by some workers to be responsive to anti-renin agents[11] while other forms of essential hyperten-

sion with low levels of circulating renin and angiotensin II (low renin hypertension) have not.[12]

The results obtained so far have prompted the following hypothesis. Propranolol responsiveness which has been uniform and impressive in this family suggests that their hypertension is renin-dependant, which implies that there might be an over-activity somewhere along the renin-angiotensinogen-hormonal system determined by the homozygous state of the hypertensive gene. Further work envisaged would include testing of the hypothesis by measuring renin and angiotensin levels in both hypertensive and normotensive members of this family and exploiting these genetic findings to design clinical-pharmacological and biochemical tests for the identification of the heterozygote for purpose of genetic counseling and for the early diagnosis of the homozygous under 30 whose blood pressure may be normal. Further work is also planned on living members of the family tree to see the relationship if any of G-6PD deficiency on the age at which hypertension manifests itself in these people, one in four of the males being expected to carry x^- gene in Ghana.

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