

Absence of hypertensive retinopathy in a Turkish kindred with autosomal dominant hypertension and brachydactyly

Lars-Olof Hattenbach, Hakan R Toka, Okan Toka, Herbert Schuster, Friedrich C Luft

Abstract

Background—A 60 member Turkish kindred with autosomal dominant hypertension, which cosegregates completely with brachydactyly and short stature, was studied. Affected people have severe hypertension and generally die of stroke by the age of 50. The hypertension closely resembles essential hypertension and, accordingly, the mechanisms of blood pressure elevation are unknown. The gene responsible was mapped to chromosome 12p.

Methods—All 29 affected family members underwent a basic physical examination and funduscopy. Other than markedly elevated blood pressures and the residua of stroke in a few subjects, the apparent lack of end organ damage was striking, including the normal appearing fundi. Five affected individuals were studied in a clinical research unit study. All underwent a complete ophthalmological examination. Fluorescein angiograms were obtained in three subjects.

Results—Systolic blood pressures ranged from 170 to 250 mm Hg, while diastolic blood pressures ranged from 100 to 150 mm Hg in affected individuals. In all affected subjects, the fundi were only minimally altered or clinically normal. All three fluorescein angiograms were normal. Despite severe hypertension since childhood the patients showed no signs of hypertensive retinopathy.

Conclusions—The absence of hypertensive retinopathy in this novel form of inherited hypertension is due to an altered structure of retinal arteriolar walls or some other protective mechanism. Since evidence of end organ damage is scarce in other organs as well, the protective mechanism appears to be generalised.

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Monogenic hypertension provides an opportunity to study blood pressure elevation resulting from a single mechanism. Examples include glucocorticoid remediable aldosteronism, Liddle syndrome, and the syndrome of apparent mineralocorticoid excess.¹ In these conditions, salt and water retention is directly responsible for the elevated blood pressure and the renin-angiotensin system is suppressed. We recently studied a large family with autosomal dominant monogenic hypertension first described by Bilginturan *et al.*² We mapped the gene responsible to chromosome 12p.³ In this family, all affected

members have brachydactyly and are on average 10 cm shorter than non-affected individuals. The hypertension, which begins in childhood, is severe and results in death from stroke at the age of 50. The renin-angiotensin system and circulating catecholamines respond normally in affected family members and they are not salt sensitive. We were struck by the relative absence of end organ damage in affected individuals and particularly by their nearly normal funduscopic examination.⁴ We were able to study five individuals in more detail.

Patients and methods

After obtaining written informed consent in the Turkish language, we examined all 60 family members, 29 of whom had brachydactyly.³ The blood pressures were taken for 10 minutes supine with an oscillometric automated device. All adults with brachydactyly met the criteria for hypertension—namely, >130/90 mm Hg in men aged <45 years, >140/95 mm Hg in men >45 years and >160/95 mm Hg in adult women of all age groups.⁵ In children with brachydactyly, the blood pressures were >115/84 mm Hg in subjects aged 5 years, >130/92 mm Hg in subjects aged 10 years, and >138/95 mm Hg in individuals by the age of 15 years (all above the 95th percentile).⁶ All family members without brachydactyly had blood pressures below these criteria.

Five affected individuals, two men aged 46 and 31 years and three women aged 40, 31, and 30 years, agreed to come to our clinical research unit in Berlin. Details on the clinical and laboratory examinations are outlined elsewhere.⁴ The visual acuity was assessed, bilateral slit lamp examinations were performed, and the optic fundi were examined. The presence of retinopathy was defined as generalised or localised arteriolar narrowing, arteriovenous crossing abnormalities, the presence of retinal haemorrhages and/or hard exudates, cotton wool spots, venous beading, disc oedema, and retinal new vessels. Mild fundus changes were defined as arteriolar narrowing or tortuosity and arteriovenous nicking. The ophthalmoscopic findings were documented by fundus photography. Additionally, fluorescein angiography was performed in three affected individuals and evaluated for the presence of peripapillary leakage, macular oedema, microaneurysms, and areas of capillary non-perfusion. The photographs and fluorescein angiograms were reviewed by two independent observers, who were not aware of the patient's classification or blood pressure values.

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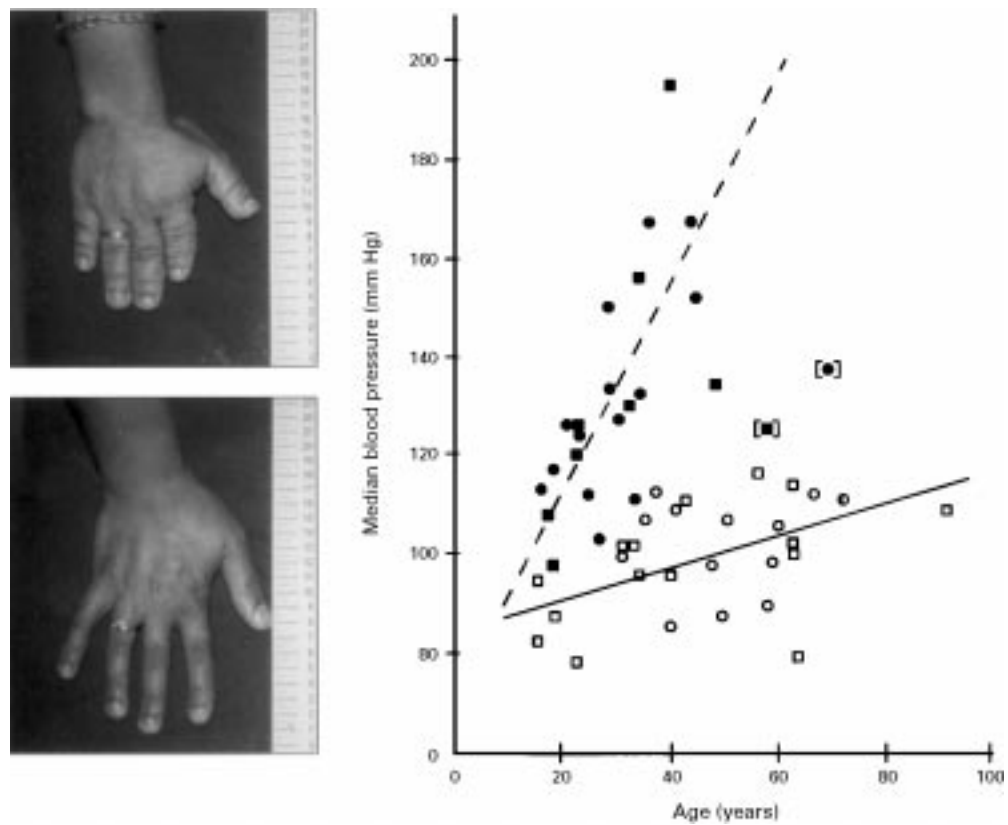


Figure 1 The left panels show the brachydactyly (type E) from an affected person (upper) compared with the hand of a non-affected sibling (lower). Hypertension and brachydactyly cosegregate 100%. The right panel plots age and mean arterial blood pressure. Affected individuals are indicated by solid symbols (squares, males; circles, females) while non-affected individuals are represented by open symbols. The blood pressure increase with age is striking, as is the fact that affected individuals, unless treated, die of stroke at around 50 years of age.

Results

Figure 1 shows the hands of two adults, an affected woman and her non-affected sister. Also shown is the influence of advancing age on mean arterial blood pressure in members of this kindred. By the age of 50, affected individuals had a mean arterial blood pressure >150 mm Hg, while non-affected individuals had a mean arterial blood pressure of <100 mm Hg. The physical examinations performed in Turkey by an experienced internist showed few hypertensive sequelae. In particular, cardiac enlargement was subtle if present and the optic fundi of those affected were normal or only minimally altered in older individuals. Two family members showed neurological evidence of stroke residua. We were able to review a computerised tomographic scan from one subject and a magnetic resonance image from the other. One subject had had a lacunar infarct and the other had findings consistent with a small intracerebral haemorrhage. Urinalyses were performed and showed no gross proteinuria. A few affected adults had microalbuminuria as did several non-affected older people.

The five affected and one unaffected family members, who were examined in Berlin, all showed normal findings on slit lamp examination. The corneas were unremarkable and no lenticular abnormalities were visible. In the five affected people, the visual acuity was normal and ranged from 20/25 to 20/20. In one subject the visual acuity was decreased in one eye. This change was not related to any morphological

finding. Instead, a history of strabismus in childhood was elicited as a possible cause of amblyopia. In the older affected patients, only minimally discernible fundus changes were observed—namely, mild arteriolar narrowing and tortuosity. The fundus photograph of the most severely affected family member in this study is shown in Figure 2 (upper panel). He is a 46 year old man with a blood pressure of 250/150 mm Hg that had not been treated until 2 years earlier when he had a myocardial infarction. In the research unit his 24 hour ambulatory blood pressure measurement showed diastolic blood pressure values consistently above 150 mm Hg without a nocturnal dip. He is the only member of the family with coronary disease, perhaps related to his markedly elevated serum Lp(a) lipoprotein concentrations. His fluorescein angiogram (Fig 2, lower panel) was normal.

Discussion

We were struck by the absence of retinopathy in affected family members, despite their impressive blood pressure elevations, which they already exhibit in childhood.²⁻⁴ In the affected man depicted here, the blood pressure was 250/150 mm Hg, but nevertheless the fundoscopic changes were minimal and may have been missed altogether had we not been alerted to their presence. We had expected severe retinopathy commensurate with the blood pressure values.⁷ Nevertheless, other signs of end organ damage in our subjects were

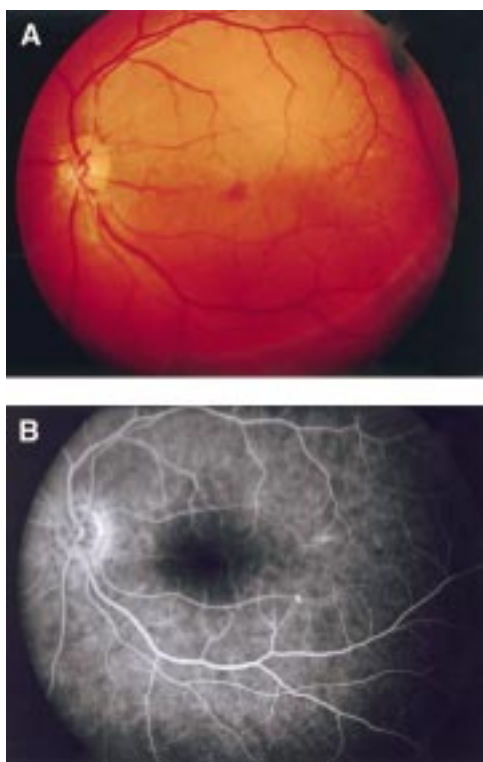


Figure 2 The upper panel shows the fundus of a 46 year old man with a blood pressure of 250/150 mm Hg. The optic disc is unremarkable, the arterioles are only slightly narrowed and tortuous, and neither haemorrhages nor exudates are present. This subject had the most prominent changes. His fluorescein angiogram, in the lower panel, was normal.

equally unimpressive. Their renal function was normal, overt proteinuria was absent, cardiac enlargement was not impressive, duplex Doppler studies of large arteries were normal, and the increase in radial wall thickness was minimal.⁴ The cause of death in affected family members is stroke; however, even the strokes appear heterogeneous. We encountered both lacunar infarct and haemorrhage, suggesting that the smaller arteries supplying the central nervous system do become diseased and eventually fail in our patients.

For good reasons, clinicians are trained to examine the optic fundi of every hypertensive patient to assess end organ damage. In the Beaver Dam Eye Study, a cross sectional population based examination, retinopathy and arteriolar narrowing were found to be common in individuals with essential hypertension.⁸ Furthermore, funduscopic changes may already be present at a relatively young age. Daniels *et al* studied children and adolescents with essential hypertension. Fifty of 95 young patients had one or more abnormality.⁹

There is evidence that the effects of systemic hypertension extend into the retinal capillary bed, causing pericyte changes with actin increase and capillary constriction.¹⁰ Cells of the retinal microvasculature show different proliferation patterns under varying oxygen

concentrations in vitro.¹¹ The mechanisms protecting the eyes and apparently also the kidneys of our subjects are not known; however, we presume that a protective pressure decrease must already be present at the level of the larger arterioles. Such vasomotor mechanisms protect the kidneys of spontaneously hypertensive rats, which are relatively resistant to the development of nephrosclerosis, compared with other genetic strains and with rats with secondary hypertension.¹² However, when one kidney is removed in these rats, proteinuria and renal damage occur, presumably because the brunt of the pressure is transmitted to the glomerular capillaries when the total renal mass is decreased.¹³ The renin-angiotensin system also apparently has a bearing on pressure transmission. Years ago, Byrom was successful in producing retinopathy and nephropathy in rats by eliciting renovascular hypertension.¹⁴

Since the gene responsible for autosomal dominant hypertension with brachydactyly has not been cloned, we do not as yet understand the mechanisms responsible for the hypertension in our subjects. We believe that elucidation of this gene will also shed light on mechanisms by which the body protects various organs from pressure induced vascular injury. The current subjects illustrate the heterogeneity in the degree of vascular damage induced by hypertension.

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