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EDITORIAL

Masked hypertension: where do we stand?

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A growing body of evidence indicates that office blood pressure (OBP) measurement alone, as performed by the physician, is not sufficient to determine a patient's true blood pressure (BP) value. Although home blood pressure (HBP) measurement or ambulatory blood pressure monitoring (ABPM) may provide us with a better estimate of a patient's BP, this may also cause problems if these two types of measurements lead to different treatment conclusions.

Most physicians are familiar with the discrepancy called white coat hypertension (WCH), which is defined as an elevated OBP value in the face of a normal BP outside the office, as determined by either ABPM or HBP. Since several studies have already shown that both ABPM and HBP correlate better with target organ damage than OBP, one may be inclined to think that WCH is rather harmless. However, some studies that evaluated the long-term effect of WCH on cardiovascular prognosis showed that subjects with WCH had an increased risk compared with normotensives, but a lower risk than those with sustained hypertension.[1] These data indicate that OBP values should not be completely ignored.

Much less is known about the second discrepancy and, in fact, the opposite of WCH, namely masked hypertension (MH). Although many physicians are unfamiliar with MH, it is not a rare phenomenon as its prevalence ranges from 8 to 33% among different populations.[2,3] Some studies even found higher numbers of masked hypertensives when compared with white coat hypertensive subjects. However, it is difficult to determine the real prevalence of MH from the present literature as studies about MH vary widely in definitions, equipment used, populations and measurement procedures. This also holds true for the paper by Aksoy *et al.*[4] in the present issue of the Journal. In this paper the authors dealt with the prevalence of MH among 57 seemingly well-controlled, treated hypertensive patients and 31 untreated normotensive subjects. They found that MH occurred frequently in the hypertensives but not in the normotensives, although in some normotensive subjects there was a clear difference between OBP and HBP. However, the OBP procedure, as performed by Aksoy and co-workers, is rather unusual. The time before the first duplicated measurement was taken and the time between the other duplicated measurements amounted to ten minutes. When such a long time elapses before measurements are taken, the white coat effect will become smaller.[5] Consequently, when patients are sitting longer in a chair before the OBP is taken, they will obtain a lower OBP value as compared with their HBP.

Another reason why we still do not know much about MH is related to the large population differences (normotensives, hypertensives, younger subjects, elderly, treated and untreated subjects) among studies that have investigated MH. The study by Aksoy and co-workers shows that there were more patients declared to have masked hypertension in the hypertensive group than in the normotensive group. This may be attributed to at least three factors. Firstly, these patients have BP values that are closer to the upper limits of the definition of MH than normotensive patients. This means that a minor discrepancy between OBP and HBP would more easily lead to a classification of MH in hypertensive patients than in normotensive individuals. Secondly, the hypertensive patients were on antihypertensive drugs that they may have taken in the morning. HBP was performed in the early morning, at the 'trough' moment of the antihypertensive activity of the medication. OBP was regularly performed in a range of two to eight hours after drug intake so that it might already have had its influence on the BP. Thirdly, the percentage of men in the studies differs between both groups (47% in the group with treated hypertensives and 71% in the group with healthy volunteers). Indeed, some studies have shown that the prevalence of MH was higher among females than among males; however, other

[**]Th. Thien was not involved in the handling and review process of this paper.

studies found the opposite. Nevertheless, because of these differences in gender percentages between the two groups one should be careful when drawing conclusions from between-group comparisons.

In most studies OBP was performed with a mercury sphygmomanometer, which is highly susceptible to observer bias, while HBP was commonly performed with an automatic oscillometric device. Observer bias reduces reliability of the obtained BP values while employment of different measurement devices further complicates comparisons between OBP and HBP. Therefore, Aksoy and co-workers did do well to perform all measurements with the same device: the Omron 705CP automatic device. However, for validation of the BP device used, the European Society of Hypertension (ESH) and the British Hypertension Society (BHS) allowed inaccuracy to 5 mmHg.[6] This inaccuracy of the device should have been taken into account for analysis. Therefore, it is worth recommending the use of a 'grey zone' and allowing, for example, for 10 mmHg systolic and 6 mmHg diastolic BP differences between the OBP and SBP values. In that case MH would be defined as an HBP value that is at least 10 mmHg systolic and 6 mmHg diastolic higher than the OBP value.

Overall knowledge of MH would significantly improve if all studies followed the same guidelines for BP measurement procedures and used the same validated oscillometric measurement device for both OBP and HBP. This would prevent observer bias and facilitate comparison between the procedures.

The overall accepted definition of MH is the one recommended by the ESH[7] (an OBP value <140/90 mmHg and an HBP value ≥135 mmHg systolic and/or 85 mmHg diastolic). Aksoy and co-workers also determined MH according to the ESH definition. They used the first of the duplicated office measurements as the OBP value, which led to more patients above the OBP limit (this decreases the MH prevalence) and naturally more patients had BP values above the HBP limit as the threshold decreased from 140/90 mmHg to 135/85 mmHg (this increases the MH prevalence). Together, this resulted in a higher MH prevalence than the previous definition (37 *vs* 28%). Although the ESH definition is commonly accepted, it is remarkable that patients can be classified as masked hypertensives when they obtain similar OBP and HBP values (e.g. 138/86 mmHg). This may be a reason to revise the ESH definitions, also because they assume that a physician will perform the OBP with a mercury sphygmomanometer and the HBP is assessed with an automatic oscillometric device. Since Aksoy and co-workers used the same oscillometric device for OBP and HBP, differences in BP values could not result from the device. Therefore, their first definition of MH seems to be the most appropriate one.

The explanation for MH has been sought in factors that increase daytime ambulatory blood pressure such as physical activity, stressful conditions, tobacco and coffee,[8,9] alcohol,[10] sedentary habits[11] or greater reactivity to daily life stressors.[12] However, MH could, of course, also be due to an exceptionally low OBP in the face of increased HBP or ABPM values. Low OBP values can be due to a postprandial dip or previous antihypertensive drug intake. Therefore, when patients take antihypertensive treatment it is absolutely essential to instruct patients carefully on how to take their drugs and verify, at each visit when OBP is performed, if and how their treatment was taken. Despite all speculations, the true identity of MH has not yet been revealed as the reproducibility of MH has not been investigated until now.

Since ABPM and HBP are better risk predictors than OBP,[13-19] patients with MH, both treated and untreated, exhibit a cardiovascular risk similar to that of sustained hypertensive patients. When subjects have MH and their treatment is based on OBP results, these patients will not receive the treatment they should. For this reason it would be desirable if all patients performed HBP in addition to OBP. However, for practical reasons it is impossible to let all patients perform HBP. Therefore, HBP should be recommended, in particular, for patients with high cardiovascular risk or with symptoms possibly related to their BP level, or when there is a discrepancy between BP values and degree of target organ damage. Eventually, an additional ABPM could be performed to determine the most appropriate treatment if a discrepancy is found between OBP and HBP values.

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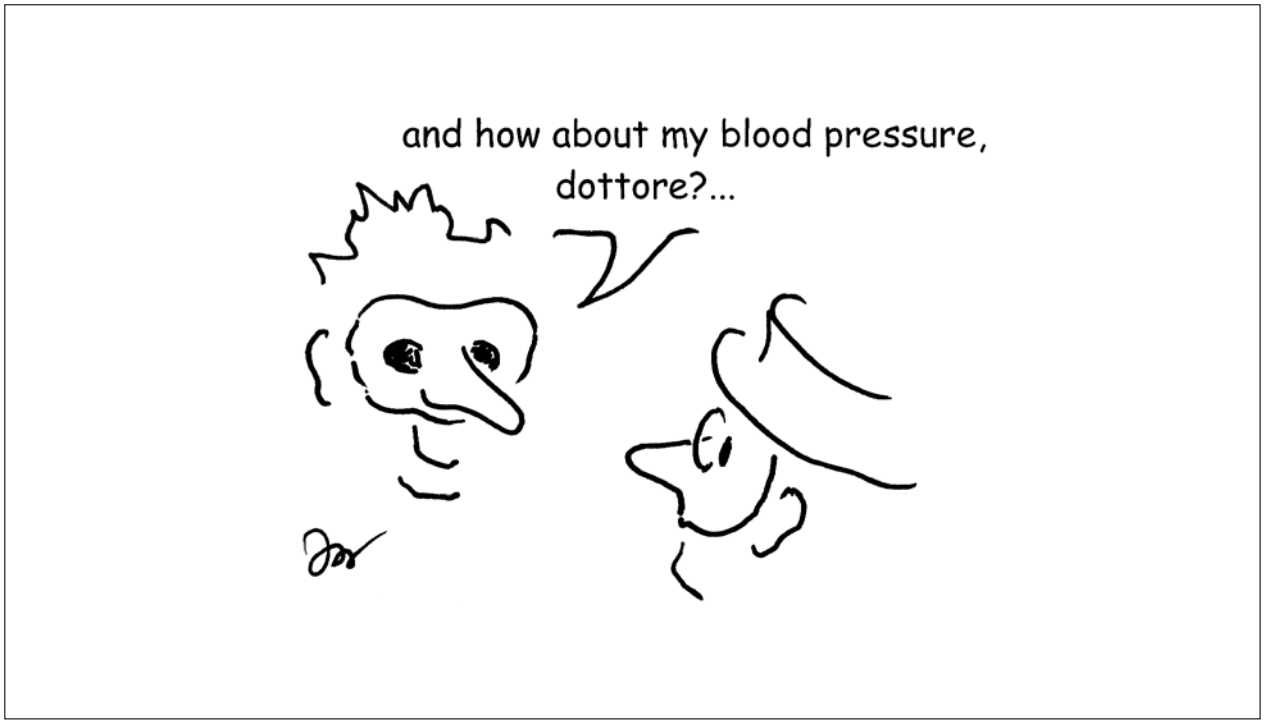

Verberk, et al. Masked hypertension.

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REVIEW

Overview on visceral manifestations of mitochondrial disorders

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ABSTRACT

Mitochondriopathies (MCPs) that reach adult age not only manifest in the central and peripheral nervous systems, eyes, ears, and dermis, but also in visceral organs, such as endocrine organs, heart, liver, guts, kidneys and blood. Visceral manifestations occur as part of a multisystem involvement or rarely as single organ affection. Endocrinological abnormalities are found in the MELAS, MERRF, KSS, MIDD and DIDMOAD syndromes. Cardiac involvement occurs in the MELAS, MERRF, KSS, CPEO, LHON, NARP, and Leigh syndromes. Gastrointestinal manifestations are common in the MERRF, MNGIE, DIDMOAD, and Leigh syndromes. Mitochondrial syndromes with renal manifestations are the KSS, Pearson, DIDMOAD, and Leigh syndromes. The haematopoetic system is affected in the KSS, MERRF, and Leigh syndromes. In addition, visceral manifestations are found in many nonsyndromic MCPs. Although there is no causal therapy for MCPs, adequate symptomatic therapy, particularly of visceral manifestations, markedly improves quality of life and prognosis of these still often neglected or overlooked disorders.

KEYWORDS

Internal medicine, mitochondrial, neuromuscular, respiratory chain, visceral organs

INTRODUCTION

Mitochondriopathies (MCPs) were long regarded as disorders affecting almost exclusively the peripheral or central nervous system (encephalomyopathies). However, it turned out that MCPs are multisystem disorders in the majority of cases, also affecting eyes, ears, endocrine organs, heart, guts, liver, kidneys, blood, and dermis.[1-3] Since MCPs may cause any symptom, in any organ, at any age, the clinical presentation is quite heterogeneous. In rare cases only a single organ is affected, but multisystem involvement may develop with progression of the disease. Possible manifestations of visceral organs are summarised in *table 1*. Various combinations of organ involvement led to the definition of mitochondrial syndromes, of which some are well known for their acronyms. The majority of MCPs, however, do not fit into one of these disease categories. Mitochondrial syndromes with visceral manifestations are listed in *tables 2* and *3*.

AETIOLOGY

MCPs are either due to genetic causes (primary MCPs) or to nongenetic endogenous or exogenous disturbances of mitochondrial functions (secondary MCPs). Genetic

Table 1. *Visceral manifestations of mitochondriopathies*

Endocrinological system Hypopituitarism, short stature, diabetes insipidus, hypothyroidism, hypoparathyroidism, hyperparathyroidism, hyperthyroidism, polyphagia, polydypsia, hyperhidrosis, insufficiency of the suprarenal gland, hyponatriaemia, hypokalaemia, hyperlipidaemia, amenorrhoea, hypogonadism, gynaecomastia, sicca syndrome, osteoporosis
Heart Cardiomyopathy, rhythm abnormalities, left ventricular hypertrabeculation, Takotsubo phenomenon
Gastrointestinal Paradontosis, dysphagia, gastrointestinal dysmotility, pseudo-obstruction, recurrent vomiting, hepatopathy, recurrent pancreatitis, exogene pancreas insufficiency, villous atrophy, malabsorption, diarrhoea, weight loss, anorexia
Kidneys Renal cysts, tubulopathy, focal-segmental glomerulosclerosis,[21] Toni-Debre-Fanconi syndrome
Blood Anaemia, leucopenia, thrombocytopenia, eosinophilia

Table 2. *Syndromic mitochondrial mitochondriopathies with visceral manifestations*

Acronym	Translation	Endocrine organs	Heart	Guts	Kidney	Blood
CPEO	Chronic progressive external ophthalmoplegia	N	Rhythm abnormalities	N	N	N
KSS	Kearns-Sayre syndrome	Short stature, diabetes, delayed puberty Hypoparathyroidism, osteoporosis, amenorrhoea Hashimoto thyroiditis	Rhythm abnormalities Dysphagia	Hepatopathy	Toni-Debre-Fancon syndrome Anaemia	Megaloblastic
MELAS	Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes	Short stature, diabetes	Dilative cardiomyopathy, LVHT	Vomiting	N	N N
MERRF	Myoclonic epilepsy and ragged red fibres	Short stature, diabetes	Cardiomyopathy Rhythm abnormalities	Pseudo-obstruction Steatosis hepatis	N	Pancytopenia
MIDD	Maternally inherited diabetes and deafness	Diabetes	N	N	N	N
LHON	Leber's hereditary optic neuropathy	N	Rhythm abnormalities, LVHT	N	N	N
NARP	Neurogenic muscle weakness, ataxia, retinitis pigmentosa	N	Cardiomyopathy	N	N	N
MILS	Maternally inherited Leigh's syndrome	Lactacidosis	Hypotonia	Vomiting	N	N

LVHT = left ventricular hypertrabeculation; N = no manifestation.

Table 3. *Syndromic and nonsyndromic nuclear mitochondriopathies with visceral manifestations*

Syndrome	Mutated gene(s)	Inner organ manifestation
Mutated respiratory chain complexes		
Leigh's syndrome	NDUFS1, NDUFS4, NDUFS7 NDUSF8, NDUFV1, SDHA, CoQ10	Hypotonia, vomiting, cardiomyopathy
Cardioencephalomyopathy syndrome	NDUFS2	Cardiomyopathy
NN	SDHB	Pheochromocytoma, cervical paraganglioma
NN	SDHC, SDHD	Hereditary paraganglioma
Mutated assembly factors		
Leigh's syndrome	SURF1, LRPPRC	Hypotonia, nomiting, hypertrophic cardiomyopathy
NN	SCO1	Ketoacidotic coma, hepatopathy
NN	SCO2	Cardiomyopathy
NN	COX10	Tubulopathy
NN	COX15	Hypertrophic cardiomyopathy
NN	BCS1L	Neonatal proximal tubulopathy, hepatopathy[73]
Mutated proteins responsible for mtDNA stability (depletion and multiple deletions of mtDNA)		
MNGIE	TP	Osteoporosis, malabsorption, gastroparesis, pseudo-obstruction, gastrointestinal dysmotility
MDS	DGUOK	Hepatopathy
DIDMOAD (Wolfram's syndrome)	WFS1, WFS2	Diabetes mellitus, diabetes insipidus, optic atrophy, deafness, dysmotility, hypopituitarism, hypogonadism
Mutated factors involved in the biogenesis of mitochondria		
Ataxia/sideroblastic anaemia syndrome	ABC7	X-chromosomal, sideroblastic anaemia
Barth's syndrome	TAZ	Cardiomyopathy, LVHT, neutropenia, short stature, glutaconic aciduria
Friedreich's ataxia	FRAXA	Hypertrophic cardiomyopathy
Mohr-Tranebjaerg syndrome	DDP1	Deafness, dystonia, cortical blindness, cataract, spasticity, dysphagia

CoQ = coenzyme Q; NN = no name; SDH = succinate dehydrogenase gene; SURF = surfeit locus protein; LRPPRC = leucine-rich pentatricopeptide motif containing protein; COX = cytochrome-c-oxydase; BCS1L gene = human bc1 synthesis-like gene; mtDNA = mitochondrial deoxyribonucleic acid; MNGIE = neurogastrointestinal encephalomyopathy, TP = thymidin phosphorylase; MDS = mitochondrial depletion syndrome; DGUOK = deoxy-guanosine-kinase; DIDMOAD = diabetes insipidus, diabetes mellitus, optic atrophy, deafness; WFS = Wolfram's syndrome; TAZ = taffazin; LVHT = left ventricular hypertrabeculation; FRAXA = frataxin; DDP1 = deafness dystonia protein 1 gene.

causes of MCPs are mutations in genes of either the mitochondrial deoxyribonucleic acid (mtDNA) or the nuclear deoxyribonucleic acid (nDNA),[4] indirectly affecting mtDNA or mitochondrial function ('nuclear' MCPs).[5] In adults half of the MCPs are due to mtDNA mutations and the other half to nDNA mutations.[2] In children, the percentage of nuclear MCPs is estimated to be 80%.[6] Mitochondrial and nuclear MCPs may be either sporadic or inherited. Inherited MCPs may be transmitted via an autosomal dominant, autosomal recessive, X-chromosomal, or maternal trait. The most widely appreciated mode of inheritance is that via the maternal line. Maternally inherited mtDNA mutations may simulate dominant traits because of reduced penetrance or complex interaction with genetic and environmental factors.[4] Dominant traits are rare in MCPs and affect the organelle biogenesis and the integrity of the mtDNA, resulting in impaired energy supply, abnormal mitochondrial trafficking, increased toxic damage by oxygen radicals, and mitochondrially driven apoptosis.[4] Both haploinsufficiency and gain-of-function mechanisms underlie nuclear MCPs.

Mitochondrial DNA mutations

Human mtDNA is a 16.5kb circular minichromosome consisting of two complementary strands (H and L strand). MtDNA contains 13 mit genes encoding for subunits of the respiratory chain complexes I (NADH dehydrogenase (ND)1-4, ND4L, ND5-6), III (cytochrome b), IV (cytochrome-c-oxydase (COX)I-III) and V (adenosine triphosphatase (ATPase) 6, ATPase8), and 24 syn genes encoding for 22 tRNAs (ribonucleic acid) and two rRNAs.[1] Only the D-loop is a noncoding stretch, containing the promoters for L and H strand transcription. All coding sequences are contiguous with each other without introns.[2] Since the mtDNA genetic code differs from the universal code, the expression of mtDNA genes relies on the specific mitochondrial protein synthesis, depending on the interplay between nuclear encoded transcriptional and translational factors with mitochondrial tRNAs and rRNAs.

Mitochondrial genetics differs from nuclear genetics in the following points:

1. Mitochondrial DNA is maternally inherited.
2. Mitochondria are polyploid, containing 2-10 mtDNA copies per organelle, and each cell contains hundreds of mitochondria.
3. All mtDNA copies are identical (homoplasmy). The propensity of mtDNA to mutate randomly, however, results in the coexistence of wild-type mtDNA and mutant mtDNA in a single cell and organ (heteroplasmy).
4. Mitochondria and mutant mtDNA are stochastically distributed to daughter cells, resulting in changing mutation loads in different generations and increasing the phenotypic variation of MCPs (bottleneck effect).
5. Because of mitotic segregations and polyploidy phenotypic expression is dependent on a threshold effect. If the load of mutant mtDNA copies exceeds a certain amount, the effect of a mutation can no longer be compensated by wild-type mtDNA.
6. Phenotypic variability is additionally dependent on the pathogenicity of a mutation, the affected gene, the mutation load and its tissue distribution, and the reliance of an organ on the mitochondrial energy supply. Organs that predominantly rely on mitochondrial energy production are the eyes, ears, central and peripheral nervous systems, heart, endocrine system, kidney, guts and liver.

MtDNA mutations are divided into large-scale rearrangements (partial deletions or duplications) and inherited point mutations. Large-scale rearrangements are usually sporadic, while point mutations are usually maternally inherited. Large-scale rearrangements affect several genes and are invariably heteroplasmic, whereas point mutations affect mit and sin genes and can be heteroplasmic or homoplastic.[1,2,4,5] Phenotype expression of mtDNA mutations often requires the influence of nuclear modifier genes, environmental factors, or the presence of mtDNA haplotypes (polymorphisms). Clusters of mtDNA variants might act as predisposing haplotypes, increasing the risk of disease.[7]

Nuclear DNA mutations

Nuclear genes involved in the development of MCPs can be subdivided into four groups: genes encoding for structural components of the respiratory chain; genes encoding for assembly factors of respiratory chain complexes; genes responsible for the mtDNA stability; and genes involved in the biogenesis of mitochondria (*table 3*).[2] Generally, the phenotype-genotype correlation in MCPs is poor.[1]

DIAGNOSIS

Diagnosing MCPs is a challenge because of their wide clinical and genetic heterogeneity.[8] Generally, the diagnosis is based on clinical, blood chemical, electrophysiological, imaging, histological, immunohistological, biochemical, polarographic, magnetic spectroscopic, and genetic investigations. Based on these investigations a stepwise strategy can be proposed for the diagnostic work-up (*figure 1*). If an adult patient presents with a classical mitochondrial syndromic MCP, such as chronic progressive external ophthalmoplegia (CPEO), Kearns-Sayre syndrome (KSS), myopathy, encephalopathy, lactacidosis and stroke-like episodes (MELAS) syndrome, myoclonic epilepsy

and ragged red fibres (MERRF) syndrome, neuropathy, ataxia, retinitis pigmentosa (NARP) syndrome, or Leber's hereditary optic neuropathy (LHON), appropriate mtDNA studies should be carried out as a first-line investigation. If the phenotype is classic for a nuclear syndromic MCP (Leigh's syndrome, myoneurogastrointestinal encephalopathy (MNGIE)), nDNA genetic studies should then be performed (*figure 1*).[9]

If the patient presents with nonsyndromic MCP, it is advisable to individualise the diagnostic approach.[10,11] since there is no golden standard for diagnosing MCPs and since the majority of MCPs are sporadic. If the phenotype is nonsyndromic, but highly suggestive of encephalomyopathy, blood, urine or cerebrospinal fluid (CSF) studies should first be carried out and if negative, followed by a muscle biopsy for histological, immunehistological, biochemical, or polarographic investigations (*figure 1*).[9,12] If these investigations yield negative results, but there is still suspicion of a mitochondrial MCP, sequencing the entire mtDNA should be considered. Myopathy with or without hyper-creatine-kinase-aemia or lactacidosis is the most common presenting feature.[13] Phenotypes suggestive of MCP include the combinations deafness, cardiomyopathy and diabetes together with encephalomyopathy,[1] short stature, deafness, and ptosis,[9] or leucencephalopathy of undetermined cause, particularly if ischaemia, multiple sclerosis, and leucodystrophy have been ruled out.[14] Concerning muscle biopsy, COX staining alone is not sufficient to assess the respiratory function immunohistochemically, which is why it should be always complemented by succinate dehydrogenase (SDH) staining. Generally, MCP should be considered when there is an unexplained association of abnormalities with progressive course, involving seemingly unrelated organs.[11] Several research groups have developed diagnostic criteria, which may be useful for diagnosing MCPs.[8,15-17]

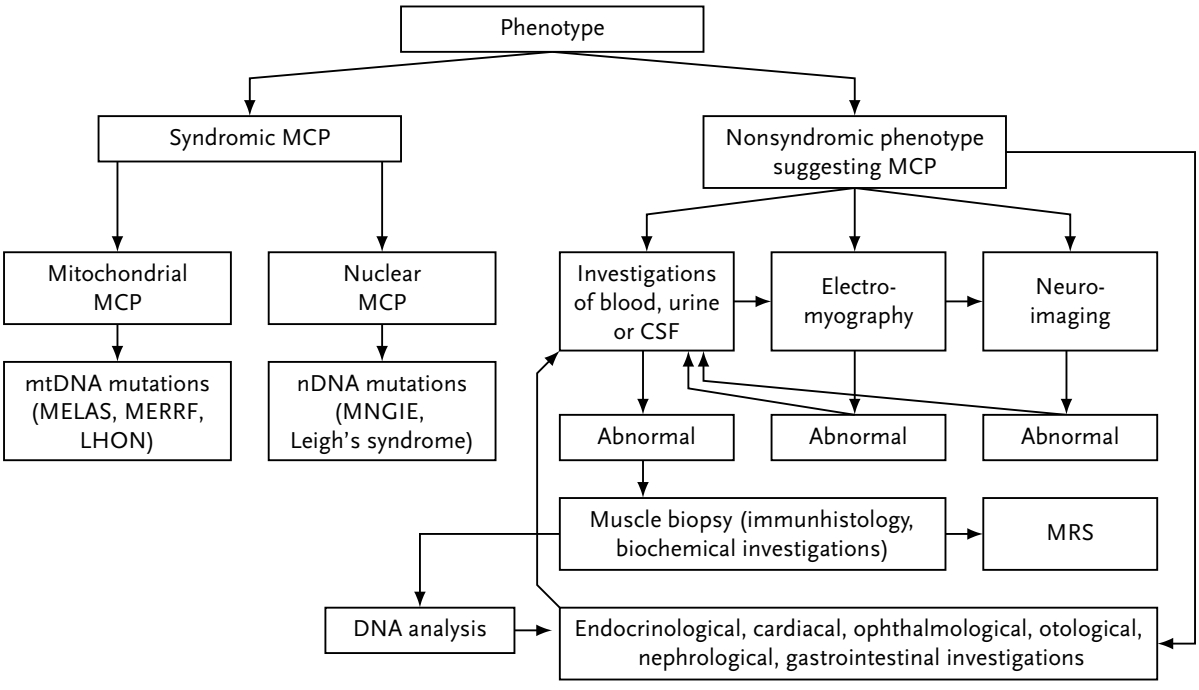
VISCERAL MANIFESTATIONS OF MITOCHONDRIOPATHIES

Visceral manifestations of MCPs concern the endocrine organs, heart, guts, liver, the kidney, and the haematopoetic system. In addition to the classical mitochondrial syndromes, which are accompanied by visceral manifestations,[18] phenotypes that do not fit into one of the known mitochondrial syndromes account for the majority of MCPs with visceral manifestations.

ENDOCRINE ORGANS

Endocrinological abnormalities represent the most frequent visceral manifestations of MCPs. Endocrine organs affected in MCPs are the pituitary gland (hypopituitarism with growth retardation, thyroid

Figure 1. *Stepwise procedure for the diagnostic work-up of mitochondriopathies*



dysfunction, hypocorticism, gonadal dysfunction, and abnormalities in the water homeostasis), the thyroid gland (hypothyroidism, hyperthyroidism, Hashimoto thyroiditis), the parathyroid gland (hypo- or hyperparathyroidism), the endocrine pancreas (mitochondrial diabetes mellitus), the suprarenal gland (insufficiency with hypoaldosteronism, (hyponatriaemia) or Addison's syndrome (hypotension, eosinophilia)), or the gonads (impotence, infertility, spontaneous abortion). Symptoms of hypopituitarism or hypothyroidism may overlap with symptoms of skeletal muscle manifestations such as fatigue, general weakness, slowing, or hypotonia. Whether hyperlipidaemia, hyperuricaemia, osteoporosis, or hyperhidrosis, which are frequently associated with MCP, represent manifestations of an MCP, is unclear. Mitochondrial syndromes that go along with endocrinological manifestations are the MELAS, MERRF, KSS, maternally inherited diabetes and deafness (MIDD), and diabetes insipidus, diabetes mellitus, optic atrophy, deafness (DIDMOAD or Wolfram) syndrome (*table 2*).

HEART

The heart is the visceral organ second most frequently affected in MCPs.[9] Cardiac involvement of MCPs either manifests as impulse generation or impulse conduction disturbances or as myocardial impairment, manifesting as either hypertrophic or dilated cardiomyopathy.[19] Frequent electrocardiography abnormalities are atrial fibrillation, atrioventricular (AV) block, Wolff-Parkinson-White (WPW) syndrome, bundle branch block, QT prolongation, or ST and T-wave abnormalities. A frequently overlooked myocardial manifestation of MCPs is left ventricular hypertrabeculation, also known as noncompaction. Noncompaction presents as a meshwork of interwoven myocardial strings, all lined with endocardium, distally to the papillary muscles. On echocardiography trabeculations have the same echogenicity as the myocardium, they move synchronously with it, and are perfused from the ventricular side. In single cases apical ballooning of the left ventricle (Takotsubo's phenomenon) has been associated with MCPs. Since cardiac involvement in MCP may manifest subclinically, and rhythm abnormalities, hypertrophic/dilative cardiomyopathy, or noncompaction may be the initial or even exclusive manifestation of MCP, all these patients should undergo a complete neurological investigation. Vice versa, all patients in whom MCP is suspected or diagnosed should undergo a complete cardiological investigation.[19] MCPs are frequently associated with arterial hypertension or orthostatic hypotension. Mitochondrial syndromes, with cardiac manifestations are the MELAS, MERRF, KSS, CPEO, LHON, NARP, and Leigh syndromes (*table 2*).

GASTROINTESTINAL TRACT

Frequent gastrointestinal manifestations of MCPs are dysphagia, in case of smooth muscle affection, hepatopathy with steatosis hepatis and liver insufficiency, or villous atrophy of the small intestines with recurrent diarrhoea.[20] Rare gastrointestinal manifestations of MCPs are paradontosis, recurrent, sometimes triggerable vomiting, recurrent pancreatitis with exogen pancreas insufficiency, gastrointestinal dysmotility, gastroparesis, progressive intestinal pseudo-obstruction, abdominal pain, dilation and dysmotility of the oesophagus, stomach and the small intestines, and malabsorption with progressive malnutrition. Gastroscopy and colonoscopy often show nonspecific alterations. Gastrointestinal manifestations of MCPs are still underrecognised, most likely due to the difficult diagnostic approach. Biochemical or electron microscopic investigations of the affected organs and tissues may help to prove the impaired function or abnormal morphology of mitochondria. Mitochondrial syndromes with gastrointestinal manifestations are the MERRF, Pearson, MNGIE, DIDMOAD, Leigh, and mitochondrial depletion syndromes (MDS) (*table 2*).[20]

KIDNEYS

Renal manifestations of MCPs are polycystic kidneys, nonspecific nephritis, focal, segmental glomerulosclerosis,[21] or tubular dysfunction, which frequently turns into chronic renal failure, requiring haemodialysis. Proximal tubular dysfunction results in a more or less complete Toni-Debre-Fanconi syndrome,[3] characterised by hyperphosphaturia, hyperaminoaciduria, and glucosuria.[22] Fanconi's syndrome may occur in an isolated form as the initial manifestation of an MCP or as part of a multisystem disease.[23] Only a few patients have been reported with tubular acidosis, Bartter's syndrome, chronic tubulointerstitial nephritis, or nephritic syndrome.[3] Bicarbonaturia, hypercalcuria, proteinuria, or a decreased glomerular filtration rate may also be present.[3] Mitochondrial syndromes with renal manifestations are the KSS, Pearson, DIDMOAD, and Leigh syndromes (*table 2*).

BLOOD

Rarely, MCPs manifest in the haematopoetic system as pancreatic dysfunction or as isolated thrombocytosis or thrombopenia, or as pancytopenia. In single cases either permanent or recurrent eosinophilia can be observed, not attributable to any of the established causes. Mitochondrial syndromes accompanied by alterations of

the haematopoetic system are the KSS, Pearson, MERRF, and Leigh syndromes (*table 2*). All these manifestations are partially resistant to adequate therapy.

Syndromic, mitochondrial MCPs with visceral manifestations

Chronic progressive external ophthalmoplegia

CPEO is the commonest manifestation of mtDNA rearrangements and often associated with ptosis.[24] Later on, cataract, retinitis pigmentosa, deafness, fatigue, ataxia, limb weakness, neuropathy, rhythm abnormalities, cardiomyopathy, or renal insufficiency may develop.[14,25] The clinical course is usually benign since additional organ failure is mild and with a low risk of serious disability. CPEO is due to mtDNA deletions or point mutations in the tRNALeu, tRNAIle, tRNALys, or tRNAAsn genes.[18,26] Point mutations in the tRNALys gene cause CPEO with myoclonic epilepsy. Point mutations in the tRNALeu gene cause CPEO with multisystem involvement, CPEO with diabetes and ataxia,[18] or CPEO with myopathy and sudden death. CPEO with multiple-sclerosis-like features is due to tRNAIle mutations.[18] CPEO with diabetes and lipoma has been reported in a patient with the A3243G mutation.[27]

Kearns-Sayre syndrome

KSS is characterised by CPEO, pigmentary retinopathy, cardiac conduction defects, cerebellar ataxia, raised CSF protein, and onset before the age of 20.[28] Proximal myopathy develops with progression of the disease. Additional features may be mental retardation, deafness, syncope, bulbar symptoms such as dysphagia, stroke-like episodes, endocrine dysfunction, such as delayed puberty, primary amenorrhoea, or diabetes, sideroblastic anaemia, or lactacidosis.[25] The prognosis of KSS is poor and patients rarely survive beyond the age of 30. KSS is due to sporadic, single or multiple large-scale deletions, ranging from 1.3 to 8.8 kb or from mtDNA duplications.[18,25]

Myopathy, encephalopathy, lactacidosis, and stroke-like episodes

The commonest of the encephalomyopathies is MELAS syndrome, characterised by stroke-like episodes with hemi-syndrome, migraine, nausea, or vomiting. Additional features may be deafness, diabetes, seizures, dementia, ataxia, cortical blindness, optic atrophy, pigmentary retinopathy, dilative cardiomyopathy, exercise intolerance, lactacidosis, or short stature.[12] Many 'overlap' cases have been described with additional features, such as CPEO, myocloni, or ataxia. Stroke-like episodes are usually not disabling, often associated with migraine and do not conform to vascular territories. Stroke-like episodes are assumed to be due to metabolic derangements, spreading beyond an ischaemic focus.[1,12,29,30] Cerebral computed tomography (CT) and magnetic resonance imaging (MRI) scans typically show white matter and cortical lesions in the parieto-occipital region.[25] Uni- or bilateral basal ganglia calcifications are common. The course is slowly progressive. MELAS is due to mtDNA point mutations in tRNA, COX3, or ND5 genes or due to small-scale mtDNA deletions. A frequently detected mutation in MELAS patients is the transition A3242G. MELAS with Parkinsonism was associated with a 4bp deletion in the cytb gene.[18,31] MELAS with bilateral striatal necrosis was associated with an ND1 mutation and MELAS/LHON overlap syndrome resulted from an ND5 point mutation.[18] MELAS/MERRF overlap syndrome is due to tRNASer or tRNALys mutations.[18]

Myoclonic epilepsy and ragged red fibres

MERRF syndrome usually presents between childhood and early adulthood with photosensitive general tonic-clonic seizures, myopathy, including ptosis and ophthalmoparesis, cerebellar ataxia, dementia, and deafness. Myocloni occur alone or in association with generalised seizures. Additional features include stroke-like episodes, optic atrophy, dorsal column loss, cardiomyopathy, heart block, heart failure, respiratory failure, paralytic ileus, pancytopenia, lipomatosis, pes cavus, or polyneuropathy.[12,25] In a single case, carrying the A8344G mutation, histiocytoid cardiomyopathy was described.[32] Disease severity ranges from minor, nondisabling manifestations to progressive, ultimately fatal disease. MERRF is caused by mtDNA tRNALys point mutations or multiple mtDNA deletions resulting from nDNA mutations.[33] A mutation frequently found in MERRF patients is the mtDNA transition A8344G.

Maternally inherited diabetes and deafness

MIDD was first described in a family with only maternally inherited diabetes and sensorineural hearing loss.[34] Later on, MIDD families were described that additionally presented with features of MELAS syndrome,[35] including seizures, migraine, short stature, mental retardation, or stroke-like episodes.[36] No correlation between the heteroplasmy rate and the clinical features was found.[36] MIDD is caused by mutations in the tRNALeu or tRNALys gene and due to large-scale tandem duplications or deletions/duplications. The most frequent mutation causing MIDD is the A3243G transition.[35-37] In a single patient the A3243G mutation was associated with hypertrophic cardiomyopathy and heart failure.[38]

Leber's hereditary optic neuropathy

LHON is the commonest cause of maternally inherited blindness in otherwise healthy young men. LHON is due to homoplasmic mtDNA mutations affecting genes, which encode for subunits of respiratory chain complex I, III, IV, or V. There are three primary LHON mutations, A3460G, A11778G, and T14484C, which account for >95%

of the cases.[13,39] Only 50% of males and 10% of females harbouring a primary LHON mutation actually develop LHON.[39] The incomplete penetrance and the predominance in males suggest that factors other than mtDNA mutations (secondary LHON mutations, nDNA mutations) play a modifying role. Onset is in late adolescence or early adulthood with subacute, painless, bilateral visual loss. Rarely, the heart (rhythm abnormalities, hypertrophic cardiomyopathy, left ventricular hypertrabeculation) or cerebrum (dystonia) are additionally affected.[1,13] Some female LHON patients present with a multiple sclerosis-like phenotype.[40] White matter lesions were also reported in a male with the A3460G mutation.[19]

Neuropathy, ataxia, retinitis pigmentosa

NARP syndrome is characterised by weakness due to motor neuropathy, sensory disturbances, cerebellar ataxia, and retinitis pigmentosa. Rare additional features include developmental delay, mental retardation, dementia, ataxia, cardiomyopathy, and epilepsy. NARP and NARP/maternally inherited Leigh's syndrome (MILS) overlap syndrome are due to mutations in the mtDNA ATPase6 subunit gene.[12,18,41]

Maternally inherited Leigh's syndrome

Leigh's syndrome, also known as subacute necrotising encephalopathy, usually presents at infancy as a multisystem disorder with brainstem and basal ganglia dysfunction, weakness, hypotonia, seizures, developmental delay, and lactacidosis. Additional features may include pyramidal signs, dystonia, optic atrophy, nystagmus, retinitis pigmentosa, ataxia, deafness, neuropathy, CPEO, or respiratory failure.[42] Visceral manifestations comprise hypertrophic cardiomyopathy, fatty infiltrations of hepatocytes, recurrent vomiting, and degeneration of the renal tubular epithelial cells.[42,43] Typical cerebral CT or MRI abnormalities include bilateral, symmetric, high-signal alterations in the spinal cord, upper brainstem, cerebellum, midbrain, thalamus, or basal ganglia, with or without cortical changes, and basal ganglia calcifications. Infantile-onset MILS is caused by ATPase6 mutations.[44] Adult-onset MILS is caused by tRNAVal mutations.[18] MILS with spinocerebellar ataxia is associated with a tRNALys mutation.[18]

Nonsyndromic, mitochondrial MCPs with visceral manifestations

Mitochondrial MCPs with visceral manifestations that do not fit into one of the established mitochondrial syndromes comprise the following entities: myopathy associated with cardiomyopathy due to tRNALeu mutations;[18] hypertrophic cardiomyopathy due to 12rRNA, tRNASIle, tRNALys, tRNAGly, or cytb mutations;[18] multisystem MCP with cardiomyopathy due to the A4269G, G8363A, C4320T mutations;[18] encephalomyopathy associated with diabetes due to the T14709C transition;[18] congenital multisystem MCP due to the A15023G transition;[18] multisystem MCP with sudden death due to the A10044G transition;[18] intestinal dysfunction associated with encephalomyopathy due to the G8313A or G1644T mutations; idiopathic sideroplastic anaemia due to the G12301A, T6721C, or T6742C mutations;[18,45] and exercise intolerance and myoglobinurea due to point mutations in the tRNAPhe, COXIII, ND4, or cytb gene.[18] MtDNA deletions and insertions may cause: diabetes, deafness, or maculopathy;[18] diabetes, deafness, and optic atrophy;[18] exercise intolerance with recurrent myoglobinuria;[18] chronic diarrhoea with villous atrophy and multisystem involvement;[18] diabetes, deafness, tubulopathy, and ataxia;[18] or diabetes, cerebellar ataxia, hearing loss, olfactory dysfunction, CPEO, and bilateral facial nerve palsy.[46]

Syndromic, nuclear mitochondriopathies with visceral manifestations

Nuclear Leigh's syndrome

Nuclear Leigh's syndrome hardly differs phenotypically from MILS. Typical clinical features are vomiting, hepatopathy, cardiomyopathy, encephalopathy, and generalised weakness. Nuclear Leigh's syndrome is caused by mutations in nDNA genes encoding for subunits of the pyruvate-dehydrogenase complex or for respiratory chain components, such as NDUFS1, NDUFS4, NDUFS7, NDUFS8, NDUFV1, or SDHA (*table 3*) or genes encoding for proteins involved in the maintenance of respiratory chain complex function by guaranteeing the correct holoenzyme assembly.[2] The most frequently mutated gene of the latter type is surfeit locus protein (SURF1), encoding for a complex IV assembling protein.[2] A French-Canadian type of Leigh's syndrome is due to mutations in the leucine-rich pentatricopeptide motif containing protein (LRPPRC) gene, encoding for a putative mtDNA transcript-processing factor.[2,47]

Myoneurogastrointestinal encephalopathy

MNGIE, also termed POLIP (polyneuropathy, ophthalmoplegia, leucencephalopathy, intestinal pseudo-obstruction), is a multisystem disorder manifesting before the age of 20 as episodic nausea, vomiting, gastroparesis, progressive intestinal pseudo-obstruction, abdominal pain, dilation or dysmotility of the oesophagus, stomach, or small intestine, diarrhoea, and malabsorption with progressive malnutrition, leading to death around the age of 40. Additional features comprise myopathy, including CPEO, glaucoma-like optic neuropathy, cognitive decline due to leucencephalopathy, retinitis pigmentosa, deafness, hoarseness, dysarthria, and polyneuropathy.[48] Post-mortem changes include visceral neuropathy (loss of neurons and fibrosis in the celiac, mesenteric, or

Auerbach plexuses) and scleroderma-like changes.[25] MNGIE was recently shown to result from mutations in a gene encoding for the thymidine phosphorylase.[33,49,50] Thymidine phosphorylase is likely to have an important role in nucleoside metabolism by regulating the availability of thymidine for DNA synthesis.[51] Accordingly, patients harbour mtDNA depletions, multiple deletions, or point mutations. Additional functions of the enzyme involve angiogenesis and cell trophism.[9] The disorder is transmitted via an autosomal recessive trait.

Diabetes insipidus, diabetes mellitus, optic atrophy, deafness (Wolfram's syndrome)

DIDMOAD syndrome is a rare autosomal recessive neurodegenerative disorder with juvenile onset, also known as Wolfram's syndrome (WFS).[52] The mortality rate of WFS is about 65% before 35 years of age. Minimal diagnostic criteria include diabetes and optic atrophy, with seemingly unknown aetiology. Other less frequent features are psychiatric abnormalities, ataxia, urinary tract atony, limited joint contractures, cardiovascular and gastrointestinal autonomic neuropathy, hypergonadotropic hypogonadism, cardiac malformations, or pituitary dysfunction.[52,53] WFS is genetically heterogeneous, but most frequently due to mutations in the WFS1 gene on chromosome 4p16 or mutations in the WFS2 gene on chromosome 4q22-24.[54,55] WSF1 and WSF2 mutations secondarily result in single or multiple mtDNA deletions.[56]

Mitochondrial depletion syndrome

MtDNA depletion of various degrees leads to a fatal multisystem infantile disorder, characterised by weakness, muscle hypotonia, CPEO, and severe lactacidosis. Additional features include hepatopathy, Fanconi's syndrome, encephalopathy, seizures, cardiomyopathy, or cataract.[12,57] Total mtDNA levels in these patients are below 35% of those in controls. No mtDNA mutations are found in these patients. The underlying defect is an impaired replication or maintenance of mtDNA due to nDNA mutations in the thymidine kinase or deoxyguanosine kinase gene, causing gastrointestinal abnormalities, deoxyguanosine-kinase (DGUOK) gene, resulting in encephalomyopathy and hepatopathy, polymerase gamma (POLG) gene causing hepatopathy with lactacidosis, WFS1 or WFS2 genes, associated with DIDMOAD syndrome, or thymidine kinase 2 gene, associated with fatal infantile hepatopathy (*table 3*).[2,19]

Barth's syndrome

Barth's syndrome is a rare X-linked disease, characterised by the triad dilated cardiomyopathy, skeletal myopathy, and neutropenia. Additionally, there may be growth retardation and 3-methyl-glutaconic aciduria. The age range is 0 to 49 years.[58] Untreated boys die in infancy or early childhood from septicaemia or cardiac failure.[59] Barth's syndrome is due to mutations in the taffazin gene on chromosome Xq28. The taffazin gene is suspected to encode for one or more acyltransferases, resulting in reduced cardiolipin synthesis and thus cardiolipin deficiency in the skeletal muscle, myocardium, and platelets.[33,58,60] Barth's syndrome is the first inborn error of metabolism identified, directly affecting cardiolipin, a component of the inner mitochondrial membrane, necessary for proper functioning of the electron transport chain.[59]

Friedreich's ataxia

Friedreich's ataxia is the most common of the inherited ataxias. Clinically, Friedreich's ataxia is characterised by cerebellar ataxia, hypertrophic cardiomyopathy, and foot deformity. Friedreich's ataxia is caused by an expansion of a GAA triplet, located within the first intron of the frataxin gene on chromosome 9q13. The mutation affects mitochondria because of its involvement in RNA processing and the intramitochondrial iron handling, leading to iron accumulation, increased sensitivity to oxidative stress, and deficient respiratory chain activity.[61] There are indications that the mutation results in a defect of iron/sulphur protein construction.[62]

Mohr-Tranebjaerg syndrome

Mohr-Tranebjaerg syndrome (MTS) is a rare disorder characterised by early-onset deafness, dystonia, cortical blindness, cataract, spasticity, dysphagia, and mental retardation.[62] MTS is due to mutations in the gene encoding for the deafness-dystonia protein (DDP1).[63] The first mutation found in this gene was the C66W missense mutation, affecting the binding of Zn(2+) via the Cys(4) motif.[64,65] As a consequence, the DDP1 molecule is incorrectly folded and loses its ability to assemble to a heterohexameric complex with its cognate partner Tim13. In a recently described patient MTS was due to the G38C transversion in exon 1 of the DDP1 gene, affecting the ATG start codon by changing methionine to isoleucine.[66] This mutation leads to the absence of DDP1 and marked reduction of Tim13. Other mutations reported were the one basepair deletion 151delT and the stop mutation E24X in the allelic Jansen's syndrome.[67] Muscle biopsy is structurally and biochemically normal, but MRI and positron emission tomography studies reveal hypometabolic areas in the right striatum, and parietal cortex and atrophy of the occipital lobes.

Nuclear chronic progressive external ophthalmoplegia

CPEO due to mutations in nuclear genes may also present with visceral manifestations, similar to those in mitochondrial CPEO. Mutated genes responsible for nuclear CPEO are due to mutations in the twinkle, ANT1, or POLG genes.[18]

Nuclear myoclonic epilepsy and ragged red fibres
MERRF syndrome is not only due to mtDNA mutations but also due to mutations in the POLG gene (nuclear MERRF).[68] The clinical features of nuclear MERRF are the same as those of mitochondrial MERRF.

Nonsyndromic, nuclear mitochondriopathies with visceral manifestations
Nonsyndromic, nuclear MCPs with visceral manifestations include fatal, multisystem complex I deficiency due to mutations in the NDUFS4 gene;[19] familial idiopathic cardiomyopathy due to multiple, secondary mtDNA deletions;[18] sideroplastic anaemia with myopathy;[18] CPEO with cardiomyopathy due to multiple, secondary mtDNA deletions;[18] thiamine-responsive megaloblastic anaemia;[17] mitochondrial diabetes;[69] pheochromocytoma and cervical paraganglioma due to SDHB mutations;[2] hereditary paragangliomas due to SDHC or SDHD mutations;[2] pyruvate dehydrogenase complex deficiency characterised by neutropenia, absent corpus callosum, absent pyramids, and ectopic inferior olives;[45] Luft's syndrome; X-linked ataxia with sideroblastic anaemia;[2,18] hepatopathy with ketoacidotic coma due to SCO1 mutations;[62] leucodystrophy with tubulopathy due to COX10 mutations;[2] and hypertrophic cardiomyopathy due to COX15 mutations.[70] Whether arteriosclerosis is a feature of MCPs remains speculative.

THERAPY

Systematic studies on therapies for MCPs are lacking. There is no causal, only symptomatic therapy of MCPs. Symptomatic therapy comprises antidiabetic therapy in case of diabetes, hormone substitution in case of other endocrine disturbances, cardiac therapy in case of rhythm abnormalities or heart failure, antiemetic drugs if there is vomiting, substitution of pancreatic enzymes, domperidone or cisapride for gastrointestinal dysmotility, substitution of potassium and sodium in case of hypokaliaemia or hyponatriaemia, hormone substitution in case of hypopituitarism, and transfusions for anaemia and pancytopenia. Symptomatic measures may markedly improve quality of life and prognosis of affected individuals. Substitution of coenzyme-Q is effective only in case of confirmed coenzyme-Q-deficiency. Idebenone has a positive influence on hypertrophic cardiomyopathy in patients with Friedreich's ataxia. If dysphagia, frequent vomiting, malabsorption, or recurrent diarrhoea leads to prominent cachexia, a percutaneous gastroenterostomy should be considered. Impaired impulse propagation in KSS or other MCPs often requires the implantation of a pacemaker already at the early stages of the disease. If there is coexisting carnitine deficiency, administration of carnitine can be helpful.[1] Ptosis often requires surgical reconstruction.

PROPHYLAXIS

More important than the administration of certain drugs is the avoidance of certain, frequently prescribed remedies, such as biguanides (cause lactacidosis), fibrates,[71] or local anaesthetics such as bupivacain or articain (inhibit respiratory chain complex I),[72,73] statins (reduce endogenous coenzyme Q10), acetyl-salicylic-acid or sevoflurane (inhibit the respiratory chain electron transport),[74,75] β-blockers (inhibit noncompetitively the ATPase and thus stage 3 respiration),[76] carvedilol (inhibits complex I,[77]), corticosteroids (reduce the transmembrane mitochondrial potential), tetracyclines and amiodarone (inhibit the β-oxidation), barbiturates, chloramphenicol (reduce mitochondrial protein synthesis and number and size of mitochondria),[45] and valproic acid (sequesters carnitine, reduces respiratory chain activity and oxidative phosphorylation),[78] doxorubicine, ifosamide, and carboplatin (cause mtDNA mutations),[79] zidovudine (causes mtDNA depletion, reduces respiratory chain complex I and IV activity),[80] and interferon (impairs the mtDNA transcription). Generally, care should be taken when applying local anaesthetics and with general anaesthesia. MCP patients also should avoid exposure to ozone.

SUMMARY

MCPs are usually multisystem disorders, which, in addition to the central and peripheral nervous systems, eyes, or ears, also manifest in visceral organs, such as endocrine organs, heart, gastrointestinal tract, liver, kidneys, or haematopoetic system. This is why the internal medicine specialist plays an important role in the diagnostic work-up and symptomatic therapy of these disorders. Internal medicine specialists should consider an MCP if a patient or family presents with a combination of endocrine dysfunctions, rhythm abnormalities, cardiomyopathy, arterial hypo- or hypertension, hepatopathy, gastrointestinal dysfunction, renal insufficiency, thrombocytopenia, or anaemia alone or in combination, without an explanation for any of these abnormalities. Since most MCPs are accompanied by neurological abnormalities, it is advisable to refer any patient with suspected MCP to a neurologist who is familiar with MCPs. All patients in whom MCP is suspected or diagnosed should also undergo ophthalmological, otolaryngological, endocrinological, cardiological, gastrointestinal, and haematological investigations. Although there is no causal therapy for MCPs, adequate symptomatic therapy,

particularly of the visceral manifestations, may result in a markedly improved quality of life and prognosis of these still often neglected or overlooked entities.

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Does masked hypertension exist in healthy volunteers and apparently well-controlled hypertensive patients?

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ABSTRACT

Background: Home blood pressure (HBP) measurement is considered to reflect BP during the day better than office BP (OBP). But in some patients HBP is higher than OBP. This is called masked hypertension (MH).

Objective: To examine whether MH occurs in healthy volunteers and apparently well-controlled hypertensives.

Methods: 57 treated hypertensive patients and 31 healthy volunteers (27/22 men) participated. Mean age (± SD) was 61 ± 13 and 29 ± 13 years, respectively. Patients were instructed to measure their BP twice daily for three days (3 readings each) with the Omron 705 CP device after at least 10 minutes rest in a comfortable sitting position. In the outpatient department, OBP was measured four times, in duplicate, every ten minutes by the physician using the same device and under similar conditions.

Results: Mean HBP of the treated hypertensive group was 146/84 ± 18/10 mmHg, significantly higher than OBP 136/79 ± 19/10 (p<0.001). For the healthy volunteer group mean HBP was 123/70 ± 15/8) mmHg and the OBP was 117/69 ± 16/10). Of 57 patients, 16 (28%) were classified as MH. The use of antihypertensive drugs was similar in the MH patients and the uncontrolled hypertensives. Logistic regression analysis showed that age tended to be a weak predictor for MH while gender, BMI and upper arm circumference were not.

Conclusion: This study demonstrates that MH occurs frequently in apparently well-controlled hypertensives, but not in healthy volunteers. However, in healthy volunteers HBP can be relevantly higher than OBP, although both values generally remain within the normotensive range.

KEYWORDS

Home blood pressure measurement, isolated ambulatory hypertension, masked hypertension, reversed white coat hypertension, white coat normotension

INTRODUCTION

It is well known that in many hypertensive patients blood pressure (BP) measured in the office by the physician (OBP) is not always representative for the average BP during the day and thus for cardiovascular risk.[1] This discrepancy has become apparent with the increased availability and use of devices for measurement of the BP at home (HBP) or ambulatory blood pressure monitoring (ABPM). Patients with a normal BP at home but an increased OBP are known as patients with isolated office hypertension, also called white coat hypertension.[2,3]

In 1992, Pickering described the reverse condition: patients who have a normal OBP but are hypertensive at home.[4] The prevalence of this phenomenon may be higher than expected. To date there is no consensus about the nomenclature for this condition. It has been called isolated home hypertension,[3] isolated ambulatory hypertension,[3] reversed white coat hypertension,[5,6] masked hypertension,[7,8] white coat normotension,[9,10] inverse white coat hypertension[11] and inverse white coat response.[12] Although Pickering originally used the term masked hypertension (MH) for untreated subjects, in most later publications[8] the term MH is also used for treated hypertensives. Therefore, in the current study we use the

#Th. Thien was not involved in the handling and review process of this paper.

term MH to indicate that a doctor will miss this condition unless HBP or ABPM is performed as well as OBP.
Most previous studies have focused on the prevalence of this condition in the general population or in untreated hypertensive patients. The present study was a pilot study to investigate if MH was, on the basis of OBP, present in healthy volunteers and in apparently well-controlled hypertensive patients.

PATIENTS AND METHODS

The patient group existed of hypertensive subjects who visited the outpatient clinic of our University Medical Centre for regular control. All hypertensive patients had been on antihypertensive drug treatment for at least one year. They were accustomed to the BP measurement procedure. The control group existed of healthy volunteers. Patients with comorbidity such as diabetes mellitus, heart failure, acute/severe diseases or autonomic failure were not included in the study. Patients with an upper-arm circumference (UAC) smaller than 22 cm or larger than 48 cm were also excluded. All patients gave written informed consent after being informed about the study. Body weight and height were measured to calculate body mass index (BMI).

Devices

HBP was measured by a validated automatic oscillometric blood pressure device, type Omron 705 CP, which is printer-equipped.[13] The inflatable bladder of the cuff had to have a width of at least 40% and a length of at least 80% of the circumference halfway between the olecranon and acromion processes. In patients with an UAC of 22 to 32 cm a normal bladder (24 x 13 cm) was used, whereas in patients with an UAC of 32 to 48 cm a larger bladder (36 x 13 cm) was used.

Study protocol

Patients were carefully instructed to measure BP twice daily (in the morning and in the evening) for three consecutive days and each measurement session consisted of three measurements. Thus in total, 18 HBP measurements were obtained. Each BP measurement was printed out and given to the doctor after the OBP measurement session. Patients were instructed to perform the BP measurements after sitting for ten minutes in a comfortable chair with arms resting on the armrest. The BP was always measured on the nondominant arm. The patients were asked to avoid talking, smoking and watching television. They were also instructed that BP measurements had to be taken after voiding and at least two hours after the meal.
After the last HBP measurements, thus always following the HBP procedure, the patients visited the doctors office and after ten minutes resting in a sitting position with their arm on the armrest, OBP was measured twice on the nondominant arm with the same device that they used at home. OBP measurements were repeated after 20, 30 and 40 minutes, resulting in a total of eight OBP measurements. These BP values were averaged and taken as the OBP for the individual patient.
In addition, auscultatory BP was simultaneously measured by a standard mercury sphygmomanometer using a Y-connector. This procedure was carried out to validate the Omron 705 CP according to the British Hypertension Society (BHS) criteria.[14] Systolic BP (SBP) was taken at phase 1 of the Korotkoff sounds and diastolic BP (DBP) at phase 5 of the Korotkoff sounds. The simultaneous BP measurement (n=528 readings) of the Omron 705 CP and the sphygmomanometer with a Y-connector resulted in grade B for SBP and grade A for DBP (British Hypertension Society protocol).[14]

Data analysis

All results are presented as mean ± SD unless stated otherwise.
Hypertension was defined as a BP of ≥140 and/or ≥90 mmHg and a normal BP as <140 and <90 mmHg. All healthy volunteers and treated hypertensive patients were categorised as follows.

- Category 1: normotensive both in the office and at home (true normotension, TN or controlled hypertension, CH).
- Category 2: hypertensive both in the office and at home (true hypertension, TH or uncontrolled hypertension, UCH).
- Category 3: hypertensive in the office and normotensive at home (isolated office hypertension, IOH, or white coat hypertension).
- Category 4: normotensive in the office and hypertensive at home. This last category was defined as masked hypertension (MH).

Differences between OBP and HBP were tested by the paired Student t-test. The association between BP category and the following factors was analysed by logistic regression analysis: gender, BMI, UAC, age, BP and heart rate.

RESULTS

The characteristics of the two groups are shown in *table 1*. Of the 57 hypertensive patients, 24 had an OBP ≥140 and/or ≥90 mmHg. HBP was stable over the three days of measurement and the evening values were constantly lower than the morning values as shown in *table 2*.
Of the 57 patients, 16 (28%) were classified as having MH as shown in *table 3a*. The OBP and HBP levels in the four groups are shown in *table 4* for the treated hypertensives.

Table 1. *Baseline characteristics of both groups*

	Treated hypertensives	Healthy volunteers
Male/female	27/30	22/9
Body mass index (kg/m²)	28 ± 4.5	24 ± 4.3
Upper arm circumference (cm)	29 ± 2.6	27 ± 3.1
Age (years)	61 ± 13.3	29 ± 13.2
Office blood pressure (mmHg)	136/79 ± 19/10	117/69 ± 16/10
Heart rate (beats/min)	63 ± 10	67 ± 11
Home blood pressure (mmHg)	146/84 ± 18/10	123/70 ± 15/8
Heart rate (beats/min)	65 ± 8	66 ± 10

Mean ± SD are presented.

Table 2. *The mean home systolic (SBP) and diastolic (DBP) blood pressure values in mmHg on the three measurement days*

	Day 1		Day 2		Day 3	
	SBP	DBP	SBP	DBP	SBP	DBP
Treated hypertensives (n=57)						
Morning	145	88	151	88	148	85
Evening	144	81	144	82	141	80
Healthy volunteers (n=31)						
Morning	122	71	120	70	121	71
Evening	124	70	124	70	125	70

Each value is the mean of all blood pressure values that were measured at that time point.

Table 3a. *Number of patients in each blood pressure (mmHg) category for the treated hypertensive group*

	OBP <140 and <90	OBP ≥140 and/or ≥90
HBP <140 and <90	n=17 (controlled hypertension)	n=4 (isolated office hypertension)
HBP ≥140 and/or ≥90	n=16 (masked hypertension)	n=20 (uncontrolled hypertension)

OBP = office blood pressure; HBP = home blood pressure.

Table 3b. *Number of patients in each blood pressure (mmHg) category for the normotensive group*

	OBP <140 and <90	OBP ≥140 and/or ≥90
HBP <140 and <90	n=28 (true normotension)	n=1 (isolated office hypertension)
HBP ≥140 and/or ≥90	n=0 (masked hypertension)	n=2 (true hypertension)

OBP = office blood pressure; HBP = home blood pressure.

In the MH group, systolic HBP was 23.6 ± 13.6 mmHg and diastolic HBP was 14.5 ± 9.1 mmHg higher than the corresponding OBP. In 11 of these 16 patients systolic HBP was even >20 mmHg higher than systolic OBP (*figure 1*), while this was the case in four patients for diastolic HBP (*figure 1*). Using the official BP thresholds for definition of hypertension diagnosis based on home BP measurement of the guidelines committee of the 2003 European Society of Hypertension-European Society of Cardiology (ESH/ESC):[15] OBP <140 and <90 mmHg together with an HBP ≥135 and/or ≥85 mmHg, as many as 21 (37%) of the patients were classified as MH. In contrast, 20 patients (35%) were uncontrolled hypertensives since they were still hypertensive both at home and in the doctors office. Obviously, the differences between HBP and OBP were smaller in this group, with systolic HBP being 4.9 ± 13.5 and diastolic HBP 2.1 ± 7.1 mmHg higher than the corresponding OBP. In only three of these 20 patients was the systolic HBP >20 mmHg higher than systolic OBP, and this was not seen at all in the diastolic HBP. In four patients both systolic and diastolic HBP were lower than the corresponding OBP and these subjects were classified as IOH. Seventeen of the 57 patients were normotensive both at home and in the office, thus called controlled hypertensives. Even in this subgroup mean HBP was higher than mean OBP (8.3 ± 9.0 and 2.8 ± 5.0 mmHg for systolic and diastolic BP, respectively).

The average number of antihypertensive drugs used in the treated hypertensive group was very similar for the four groups, as shown in *table 5*. The subgroups are small and despite this there were no relevant differences in the pharmacotherapeutic regimens between the MH and the UCH groups, but the CH group were on diuretics more often and ACE inhibitors less frequently than the UCH group.

Logistic regression analysis showed that in this study age tended to be a weak predictor (B=0.07; p=0.06) for MH in treated hypertensives while gender, BMI and UAC were not. The mean age in the MH subgroup was nearly 17 years higher than that in the CH subgroup.

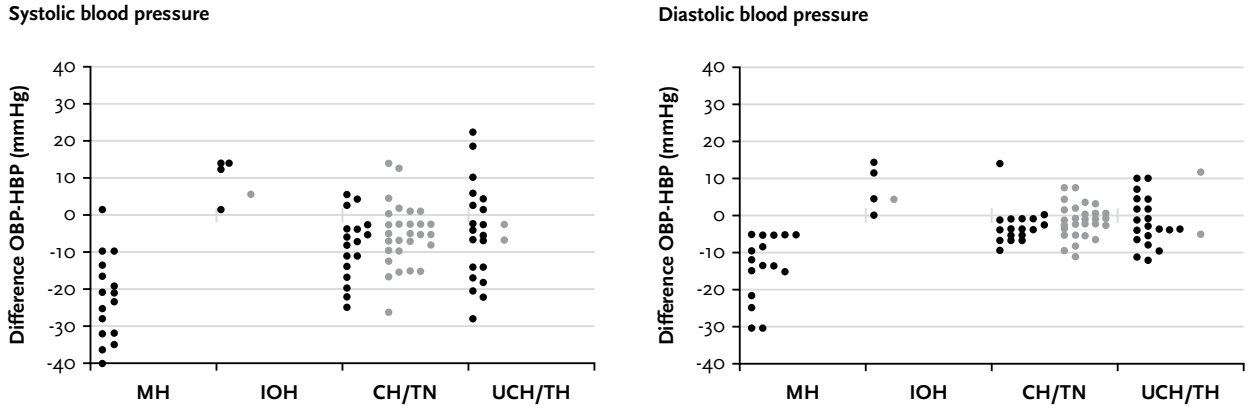
The healthy volunteers group was classified as follows: no MH (by study definition), one IOH, two TH, whereas the remaining 28 subjects were TN, as shown in *table 3b*.

Table 4. *Blood pressure (mmHg) and heart rate (beats/min) in the four groups of treated hypertensives (mean ± SD)*

	Systolic		Diastolic		Heart rate	
	OBP	HBP	OBP	HBP	OBP	HBP
Controlled hypertension	117 ± 11	126 ± 9	72 ± 7	75 ± 7	63 ± 7	65 ± 6
Uncontrolled hypertension	154 ± 15	159 ± 14	87 ± 9	89 ± 8	63 ± 11	65 ± 9
Isolated office hypertension	145 ± 4	134 ± 4	87 ± 10	79 ± 6	62 ± 4	63 ± 5
Masked hypertension	129 ± 9	153 ± 10	74 ± 7	89 ± 9	65 ± 13	65 ± 10

OBP = office blood pressure; HBP = home blood pressure.

Figure 1. *Individual data of the differences between office (OBP) and home (HBP) systolic (left panel) and diastolic (right panel) blood pressure of treated hypertensives (black dot) and healthy volunteers (grey dot)*



MH = masked hypertension; IOH = isolated office hypertension (white coat); CH = controlled hypertension; TN = true normotension; UCH = uncontrolled hypertension; TH = true hypertension.

Table 5. *Classes of antihypertensive drugs used by the patients of the four groups of treated hypertensives*

	Beta-receptor antagonists (%)	Calcium antagonists (%)	Diuretics (%)	ACE inhibitors and angiotensin-II receptor antagonists (%)	Average numbers of antihypertensive drugs
Controlled hypertension	59	41	71	29	2.0
Uncontrolled hypertension	65	30	55	55	2.1
Isolated office hypertension	75	25	75	50	2.3
Masked hypertension	63	31	56	69	2.2

ACE = angiotensin converting enzyme inhibitors.

Using the above-mentioned ESH criteria two subjects in the healthy volunteers group were classified as MH. None of the normotensive subjects were taking antihypertensive drugs. Within the healthy volunteers, there were striking differences between HBP and OBP although mostly within the normotensive range (*figure 1*).

DISCUSSION

The present study demonstrates that in this small group of apparently well-controlled outpatient clinic hypertensives a relevant percentage (28%) turned out to have hypertension at home and normotension in the office. Applying the official ESH/ESC definition[15] for the diagnosis hypertension based on home BP measurement, as many as 37% had MH.

It is difficult to compare our study with the literature because of inconsistencies in nomenclature and definitions. In addition, differences in methodology may account for disparity in results. BP was measured with the same device (tested according to the criteria of the BHS) both in the office and at home whereas in previous reports a conventional sphygmomanometer was used for the OBP measurement while in most studies another device was used for ABPM or HBP (self) measurement.[3,6,8,10,11,16]

Some but not all of the previous studies have reported that untreated patients with MH were older, more likely male, smokers, used alcohol and had higher BMI.[6,9-11,17] In our study the MH patients were older but there were no differences in BMI, BP levels and heart rate. There were no differences in the average number of antihypertensive drugs used either.

Since 1992, when Pickering *et al.*[4] described MH for the first time, several studies have reported the existence of this phenomenon,[3,5,7,9,10] and it has been suggested that the increased HBP values are due to an alerting response to the self-measurement procedure.[12] Several arguments can be raised against this suggestion. First, in the present study the same device was used both in the office and at home and the HBP levels on the three measurement days did not show any decrease as a consequence of habituation to the measurement procedure. Secondly, heart rate levels in all four groups were similar in the office and at home. Finally Parati *et al.* showed that there was no alarm reaction with the use of noninvasive BP monitoring devices.[18]

What are the possible explanations for the rather high percentage of MH? In the first place there may be a pharmacological explanation consisting of two factors: poor medication compliance at home and medication intake just before visiting the outpatient clinic so that the peak effect is observed. Although we always use long-acting medication to prevent compliance problems and we always carefully instruct and motivate our patients, we can not rule out this possibility. A second explanation is the possibility of differences in measurement conditions between office and home. Although the device was the same, BP was measured in the office four times, in duplicate, in the presence of the physician and the average was compared with the average of all home sessions on three consecutive days. However, if one looks at the four separate measurement sessions in the protocol, MH was present in 11 to 16 patients (19 to 28%), although not in the same patients in every session. As could be expected the frequency of MH was lowest in the first session, although still 19%. On the other hand the presence of the physician increases rather than decreases BP. A third explanation may be that nervous and/or older patients are less familiar with this type of technical procedure and measure a higher HBP due to a kind of stress.

In contrast to previous studies, this is one of the few reports that studied MH in treated hypertensives. In a recent retrospective study, Bobrie *et al.*[19] reported that in his study group of treated elderly hypertensives the prevalence of MH was 10.8%. In a prospective follow-up study[8] of 3.2 years they show that the MH group had the same risk for cardiovascular events as treated but insufficiently controlled hypertensives. A pivotal question pertains to whether MH carries a worse prognosis in terms of target organ damage than the patients whose BP is in the normotensive range both in the office and at home. It is generally accepted that HBP values measured by ABPM are superior to OBP values in predicting target organ damage.[5,11,20,21] If risk assessment is only based on OBP values in MH patients, the real risk is underestimated, as shown by the recent study of Bobrie *et al.*[8] In that study the cardiovascular mortality in the MH group was similar to that in the uncontrolled hypertensives and much higher than both in the isolated office or white coat hypertension group and in the controlled hypertension group. In earlier studies Liu *et al.*[10] and Sega *et al.*[3] showed that left ventricular mass index and wall thickness in patients with MH were close to that in the uncontrolled hypertension group and differed significantly from that in controlled hypertension group. Björklund *et al.*[16] showed in a longitudinal study that the multivariate hazard ratio for cardiovascular morbidity in the MH group was 2.74, while this was 3.14 in the uncontrolled hypertension group and 0.99 per 100 person-years at risk in the controlled hypertensives. So at this stage, it cannot be stated that MH is harmless. However, there are no studies about the reproducibility of MH, yet.

Of course our small study also has limitations. The protocol with the BP measurement procedure with four sessions of two readings, each time after a ten-minute rest period, is unusual in daily practice. The fixed sequence i.e. always the HBP first followed by the OBP may be considered a limitation. On the other hand, the whole protocol in all 88 subjects was performed by only one trained observer (I.A.), using the same automatic device for the OBP as used by the subjects for the HBP, thus without observer bias.

In conclusion, according to this pilot study, one should be aware that a substantial number of the apparently well-controlled hypertensives are still hypertensive at home. Therefore, without HBP measurements this condition may escape the physician's attention. However, data about reproducibility and about the prognostic significance of MH are still needed.

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ABOUT THE COVER

'Ga een vis vangen'

Els Maasson

Els Maasson studied at the Royal Academy of Visual Arts in The Hague from 1987 to 1992 and regularly exhibits her work throughout the Netherlands but also in Belgium, Japan, France and Portugal.

In recent years, Els has increasingly applied herself to the graphic technique of etching, linocutting and relief lithography. These techniques suit her the best for making her modern emblems; animal symbolic and text are the predominant themes in her work.

Els has developed her own style which, in an ironic way, plays with the suggestion of clumsiness. Using this, she talks to or rather sings to the animals in her prints.

She writes the texts for her prints herself. While writing, she lets herself be carried away by her fantasy into the dream world of animals. She looks at which characteristics of animals she would like to process herself, and shows these characteristics in her prints. The themes of humour, desire and love play an important role here. The use of text in her illustrative work also emphases the effect that the prints start to resemble illustrations from old picture books.

'The animal theme has become an integral part of my prints. I love animals as figures and shapes, but also as a personification of what lives in me, what I long for, what I love and the way in which I associate.'

The print 'Ga een vis vangen' was inspired by the following story from the bible: *In front of the gates of the city of Capernaum, on the banks of the Sea of Galilee, tax collectors demanded the temple tax from the followers of Jesus (Matthew 17:24-27). Jesus said to Peter that he should go to the sea and catch a fish. In the fish's mouth he would find a silver piece with which he could pay the tax.*

An original of this print is available at a price of € 200 and can be ordered from Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands or by e-mail: Galerie-unita@planet.nl or www.galerie-unita.com.

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ORIGINAL ARTICLE

Computerisation of endoscopy reports using standard reports and text blocks

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ABSTRACT

Background: The widespread use of gastrointestinal endoscopy for diagnosis and treatment requires effective, standardised report systems. This need is further increased by the limited storage of images, and by the need for structured databases for surveillance and epidemiology. We therefore aimed for a report system which would be quick, easy to learn, and suitable for use in busy daily practice.

Methods: Endobase III® is an endoscopy information system offering three different ways of report writing, i.e. standard reports, text blocks and Minimal Standard Terminology (MST). A working group of two university and four general hospitals worked as a reference group for the development of standard reports and text blocks. Guidelines from various gastrointestinal endoscopy societies were followed to compose the reports.

Results: Standard reports were based on a list of distinct diagnoses; text blocks were based on anatomic landmarks and individual procedures. As such, 316 standard reports were developed for upper and lower gastrointestinal endoscopy, and endoscopic retrograde cholangiopancreatography (ERCP). In this way selecting one diagnosis produces a complete report. A total of 1571 different text blocks were additionally developed for each part of the gastrointestinal tract and for procedures during endoscopy. This module allowed generation of a full report on the combination of text blocks. Reports could be composed and printed within two minutes for 90% of cases.

Conclusion: Standard reports and text blocks are a quick, user-friendly way of report writing accepted and used by a number of gastroenterologists in the Netherlands.

KEYWORDS

Computerisation, gastrointestinal endoscopy, standardised report system

INTRODUCTION

Gastrointestinal endoscopy has become a standard, widely available technique for diagnosis and treatment of gastrointestinal disorders. The number of endoscopy procedures is ever increasing as a result of, among other things, the continuous development of newer techniques, introduction of screening and surveillance programmes for gastrointestinal disorders, and the increasing incidence of a range of gastrointestinal disorders. A recent survey among endoscopists in the Netherlands showed that 325,000 gastrointestinal endoscopies are performed annually in a population of 16 million.[1] As an imaging method with numerous repetitive manoeuvres as well as findings, gastrointestinal endoscopy reports are particularly suitable for electronic storage and processing.[2] Besides this, there is a need for structured databases for surveillance, epidemiology, quality control and research. This need is further increased by the limited storage of images during endoscopy, making the report essential.

For that purpose, several endoscopy information systems have been developed in the past decade to record endoscopy findings, store images and compose reports.[3-13]

Most of these systems are standalone report systems, not suitable for implementation in a hospital information system. The combination of report writing and digital image storing is not available in all the systems. The structure of the database of most of the systems is poorly accessible for research and export of data.

There are several crucial criteria for a report system that need to be fulfilled to get it generally used, suitable for every hospital and implemented in a hospital information system.

In the further development of healthcare informatics, it is necessary for such systems to be readily acceptable for most endoscopists in a hospital unit. Secondly, it should be possible to exchange and compare data and digital images

between different consultants and hospitals. Standardised protocols should be used to communicate between different systems within a hospital based on the Health Level-7 protocol (HL-7). For exchanging images a standard format such as DICOM (Digital Imaging and Communications in Medicine) is essential.

To get the system accepted in daily practice it is crucial that first of all, data entry is fast and accurate. Thus the system has to be accessible for the computer illiterate and the learning time should be limited.[14]

Programmes using the currently available structured data entry, such as Minimal Standard Terminology (MST),[15-18] do not fulfil all these crucial criteria. Firstly, composition of a report by means of MST is usually time consuming because of the different options available. Secondly, there is a risk of getting lost in the data entry module, caused by the numerous available choices that have to be made.

Our aim was to develop a report system that is quick, easy to learn and can be used in the busy daily practice by any endoscopist. Moreover, we considered it necessary that the programme would have the capacity to build up a database with endoscopy findings for various purposes including management of surveillance programmes, and epidemiological studies and quality control. Therefore, the findings should be linked to a specific comprehensive code system. This would allow anonymous evaluation of data.

Finally, consensus of gastroenterologists from different hospitals should be achieved for use of the new report system.

MATERIALS AND METHODS

Endoscopy information system

In the latest version of Endobase III®, developed by Olympus Software, it is possible to combine different text blocks to compose a complete report besides the use of standard reports and MST.

After selecting the different standard reports, text blocks or MST the composed report can be adapted in a word processor. An extensive relational database structure has been built into the programme, thus making it suitable for storing all the different data produced in an endoscopy unit, including digital images and videos, and retract it separately with all kinds of queries. A structured data entry is also available, the MST. The MST was translated into Dutch in 1998 by our group in cooperation with Dr Delvaux during a workshop on MST.

TRANS.IT working group

At the end of 1999 a working group, the TRANS.IT project group, was founded as a peer reference group to design the standard reports and text blocks that were developed and used in the endoscopy units by the participating gastroenterologists. This group gathers on a regular basis to discuss the reports, a comprehensive coding system and new developments for endoscopy information systems.

The TRANS.IT working group consists of two university hospitals and six general hospitals and performs about 15% of all gastrointestinal endoscopies in the Netherlands. All the participants of the TRANS.IT group use the same version of standard reports, text blocks and translated MST. An alteration in the content of a standard report or text block will only be executed with the agreement of a majority of the working group members.

All the various standard reports and text blocks are directly linked to a specific code. The codes are based on the ICD-10 code system and are extended for specific endoscopy findings.[19]

Structure of an endoscopy report

Several committees of societies for gastrointestinal endoscopy have proposed guidelines to obtain a standardised format for endoscopy reports. Considering the American Society of Gastrointestinal Endoscopy's proposal,[20] the European Society of Gastrointestinal Endoscopy's amendment,[15] the advice of the Netherlands Society of Gastroenterology and our experiences with an electronic report system we developed an extended structure to an endoscopy report suitable for our endoscopy units (*table 1*). A list of items proposed by the Netherlands Society of Gastroenterology was used for the description of the findings at the investigation (*table 2*). We used this structure and the proposed items as guidelines to compose the standard reports and text blocks in our system.

Table 1. *Structure of an endoscopic report*

Patient identification data
Date of procedure
Referring doctor
Endoscopist
Assisting doctor
Instruments used
Reasons for examination
Preparation
Type of endoscopic examination
Identification number of the endoscope
Medication (anaesthesia, analgesia, sedation)
Anatomical extent of examination
Limitation(s) of examination
Findings and specimens obtained
Therapeutic intervention(s) and result(s)
Notation of images captured
Complications (during endoscopy and within 24-48 hours)
Endoscopic diagnosis
Recommendations for referring doctor
Comments
Recall letter

Table 2. *Items used to describe findings at upper gastrointestinal endoscopy*

Use mm or cm in describing the dimensions of a lesion
Findings in oesophagus. Give distance in cm from lesions to teeth
Distance of Z-line to teeth
Distance of hiatal narrowing to teeth
Aspect of contents of stomach
Peristaltic and inflation of the stomach
Findings in antral region
Findings in corpus of the stomach
Findings in cardia and fundus in retroversion
Findings in angular region
Findings in pylorus and passing
Findings in duonal bulb
Findings in proximal duodenum
Location of biopsies taken
Capture of images
Other procedures
Comment on proceedings of examination

The grading and severity of findings is classified by, for example, the Los Angeles (LA) Classification for reflux disease[21] and Forrest classification[22] for ulcers.

Prior to the examination most of the basic data of the patient necessary for the endoscopy report, such as indication, medication, endoscopist, endoscope identification number, referring doctor, general practitioner, medical history and risk factors, are already recorded in the system. The patient data can be extracted with the HL-7 protocol from the hospital information system by using the personal identification number (PIN) of the patient. Other features are recorded during or shortly after the examination date, such as *Helicobacter pylori* tests, histology or laboratory results, complications appearing after the examination and results of other gastrointestinal examinations such as ultrasonography, X-ray or manometry studies.

Presentation and selection of different text blocks

The presentation of the different standard reports and text blocks was based on the experience that endoscopists translate their findings into a diagnosis at the end of an endoscopy. To shorten the time needed to search for the corresponding diagnosis, the text blocks are presented in different subsections. First of all different text blocks were divided into anatomical regions that are easily defined during endoscopy investigations, such as oesophagus, stomach, duodenum. Within an anatomical region the possible different diagnoses are grouped, for example oesophagitis contains reflux, caustic, viral. Within these groups a classification or grading is eventually added.

All the text blocks are presented alphabetically in the programme. By typing the first characters of a diagnosis the selection of the group of diagnoses is presented.

RESULTS

Standard reports

Based on individual diagnoses, we constructed 316 different standard reports. Of these reports, 134 pertained to oesophagogastroduodenoscopy, 143 to lower digestive endoscopy, and 39 to endoscopic retrograde cholangiopancreatography (ERCP). In an open-access endoscopy unit at a district general hospital, no abnormalities are found during endoscopy in 32.3% of the endoscopy examinations.[23] Likewise in our own data, similar numbers of around 30% are found between two different referring groups.[24] The reports composed for these examinations are simple and fully standardised. Nevertheless, all the items listed in *table 2* have to be included to obtain a complete report.

The reports of the remaining 67.7% of the endoscopy examinations, where at least one abnormality was found, must also contain all items to make them complete. In some of these examinations only one abnormality was found leaving the rest of the procedures without any abnormalities. These examinations can also be reported using standard reports.

Other examinations show more abnormalities, making standard reporting less applicable. In less common combinations of abnormal or rare findings, the use of the specific text blocks is recommended.

The composed standard reports are based on the endoscopy diagnoses or a combination of diagnoses made during endoscopy (*table 3*). After the examination the endoscopist has to select this endoscopy diagnosis out of the list of different standard reports.

For reflux oesophagitis, six different standard reports have been created for the LA classification that is generally used, grade A to D and an ulcer or stricture of the oesophagus. For the frequently seen combination of columnar mucosa (Barrett) and reflux oesophagitis four additional standard reports with this combination are available.

Gastric and duodenal ulcers are described according to the Forrest classification, resulting in 30 different standard reports for a number of different locations.

Infrequent findings or findings at rare locations can be described with the use of text blocks.

The reports are alphabetically arranged in Endobase and can be searched for by giving the first one or more characters of the diagnosis.

During a normal programme at our endoscopy unit the time needed to compose a report by selecting standard reports was measured. A number of endoscopists composed a total of 291 reports in this way. A student was positioned behind the endoscopist and timed different items during report writing. The average reporting time including selection of the standard report, addition of some details in the word processor and printing of the report was 1 minute 21 seconds (SD 51 seconds) for standard reports.

Table 3. *Examples of some different standard reports for oesophagogastroduodenoscopy*

Barrett's mucosa
1. Barrett's mucosa
2. Barrett's mucosa with reflux oesophagitis grade A
3. Barrett's mucosa with reflux oesophagitis grade B
4. Barrett's mucosa with reflux oesophagitis grade C
5. Barrett's mucosa with reflux oesophagitis grade D
6. Barrett's mucosa control endoscopy
7. Barrett's carcinoma
Reflux oesophagitis
8. Reflux oesophagitis grade A
9. Reflux oesophagitis grade B
10. Reflux oesophagitis grade C
11. Reflux oesophagitis grade D
12. Reflux oesophagitis grade D with ulcer
13. Reflux oesophagitis grade D with stricture
Duodenal ulcer*
14. Duodenal ulcer, spurting bleeding (Forrest Ia)
15. Duodenal ulcer, nonspurting active bleeding (Forrest Ib)
16. Duodenal ulcer, visible vessel, no active bleeding (Forrest IIa)
17. Duodenal ulcer, nonbleeding with overlying clot (Forrest IIb)
18. Duodenal ulcer, with haematin-covered basis (Forrest IIc)
19. Duodenal ulcer, clean ulcer ground, no clot, no vessel (Forrest III)
20. Normal oesophagogastroduodenoscopy
Hiatal hernia
21. Sliding hiatal hernia
22. Sliding hiatal hernia with Cameron lesions
23. Sliding hiatal hernia and gastritis
24. Sliding hiatal hernia and gastritis and duodenitis
Varices
25. Varices oesophagus grade I
26. Varices oesophagus grade II
27. Varices oesophagus grade III
28. Varices oesophagus grade IV
29. Varices bleeding banding
30. Varices bleeding injection

*Similar standard reports for gastric ulcer.

Table 4. *Different sections for text blocks*

Oesophagogastro-duodenoscopy	Colonoscopy	ERCP
Preparation and progress of examination	Digital rectal examination	Introduction and proceedings
Oesophagus	Preparation and progress of examination	Papilla major
Stomach	Ileum	Papilla minor
Duodenal bulb	Caecum	Cannulation and pre-cut
Descending duodenum	Ascending colon	Common bile duct
Post-surgery	Transverse colon	Cystic duct and gall bladder
Therapeutic interventions	Descending colon	Bifurcation and hepatic ducts
Conclusions	Sigmoid colon	Pancreatic duct
Advice	Rectal and anal region	Sphincterotomy and balloon dilatation
	Post-surgery	Therapeutic interventions bile duct
	Therapeutic interventions	Therapeutic interventions pancreatic duct
	Conclusions	Conclusions
	Advice	Advice

ERCP = endoscopic retrograde cholangiopancreatography.

Text blocks

The text blocks were divided into different sections and presented in tabs according to different anatomical sections seen during the endoscopy and some specific parts. Reports created with text blocks were composed by selecting a diagnosis or finding from different sections of the text blocks.

For upper endoscopy eight different sections were made (*table 4*). First of all the preparation and progress of the examination was selected. Four sections were designed for the various anatomical regions: oesophagus, stomach, duodenal bulb and descending duodenum. A separate section was made for aberrant anatomy after gastrointestinal surgery. One section consisted of 'therapeutic' interventions, e.g. taking biopsies and placing endoprotheses. Another section was composed of different kinds of recommendations for the referring doctor. Finally, there was a section with conclusions which is automatically built up by the different selected text blocks.

It is possible to select one or more text blocks from each section, but also to select none and omit a section. A total of 252 text blocks were created for upper endoscopy.

Lower gastrointestinal endoscopy consists of 13 different sections (*table 4*). Again it starts with the preparation and progress of the examination. There are even different sections for anatomical regions: ileum, caecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectal and anal region. A separate section was made for digital rectal examination. There is also one section for postsurgery anatomy and a section for therapeutic interventions. Recommendations for the referring doctor are in the last section. A total of 607 text blocks were created for lower endoscopy.

Reports of ERCP mainly comprised text blocks and consisted of different anatomical and therapeutic parts (*table 4*).

Each text block consists of one or more sentences describing a diagnosis or finding of that particular text block. For this purpose a total of 1571 different text blocks have been written and are being used at this moment (*table 5*).

Table 5. *Number of standard reports and text blocks*

Examination	Number of standard reports	Number of text blocks
Oesophagogastro-duodenoscopy	134	252
Sigmoidoscopy	47	420
Colonoscopy	96	697
ERCP	39	202
Total	*316*	*1571*

ERCP = endoscopic retrograde cholangiopancreatography.

In the same way as with standard reports, the time needed to compose a report with text blocks was timed. In total 133 examinations were reported by different endoscopists and the needed time was measured. The mean time for selecting different text blocks, making some adaptations in the word processor and printing of the report was 1 minute 37 seconds (SD 55 seconds).
In comparison, the time needed to use MST was also measured in 250 reports made by an experienced user. The mean time for this way of report writing is 2 minutes and 50 seconds (SD 1 minute 10 seconds).

Coding
All endoscopy reports are coded automatically with an extension of the ICD-10. The different report systems in use all produce the same code for identical findings. In this way extensive research possibilities are created. For example, a search on 13,081 upper endoscopies for a specific ICD-10 code for duodenal ulcers (K26) results in 511 (3.9%) duodenal ulcers. This incidence is declining from 4.1% in 1996 to 2.8% in 2005. Twenty-one of these duodenal ulcers (4.1%) showed active bleeding and were classified as Forrest I, while six were Forrest Ia. Signs of recent bleeding were found with a visible vessel in 45 patients (8.8%), an overlying clot, Forrest IIb, in 31 (6.1%) and a haematin-covered basis, Forrest IIc, in 28 patients (5.5%).

DISCUSSION

Structured computerised report systems are essential for modern gastrointestinal practice. They should enable systematic, rapid, informative, comprehensive reporting of endoscopy findings and at the same time allow database handling for various purposes. Potentially, they should also be used for safety and quality control, as well as other issues including maintenance of equipment, management of stocks, and billing. In this study we have shown that a structure report system, in our setting the Endobase III® system developed by Olympus, allows incorporation of standard reports as well as text blocks. With 316 reports and 1571 text blocks, 90% of endoscopy examinations could be reported within two minutes. This makes it useful for the busy daily practice of many endoscopy units. All endoscopists in the participating hospitals use this system for report writing in every case.
Standard reports can be used to report examinations without abnormalities and examinations with frequently seen abnormalities. With rarer findings and/or a combination of diagnoses the use of text blocks is more suitable. This still makes it possible to compose a comprehensive report of the examinations performed in a short time. For those examinations (about 5 to 10%) where it is hard to compose a report with standard reports or text blocks, we propose using a standard structured data entry such as the MST. In our experience MST is more complex, takes more time and there is a risk of getting lost in the data tree. The advantage is that you can describe the findings point by point and build up a structured database.
In comparison, when using MST to compose a complete report, about 40 different choices have to be made for the description of an examination with only a few abnormalities. The possibility for the endoscopist to choose the type of report writing after the examination makes the programme user-friendly and well accepted. With standard reports and text blocks it is possible to register a standard list of all the requirements on medical records and endoscopy reports in particular.[25] With all the legal consequences nowadays, registration of endoscopy information should be as complete as possible. With this system all this information can be stored and easily retrieved.
All the standard reports and text blocks are directly linked to an extended ICD-10 code system in the database. Also other data in the system such as reason of examination, medication, and complications are coded. With these codes an anonymous database can be built with endoscopy data from different hospitals.
The standard reports and text blocks are written in Dutch, and will be translated. They are used in the Endobase system, but can be applied to any system that can work with text blocks and a code system.
All the reports and text blocks are tested and if necessary adapted by the TRANS.IT working group. The TRANS.IT working group will stay operational for at least three years, in order to improve the functionality and quality of the reports and to create a large anonymous central database. After three years we will have the possibility to answer specific research questions from the results of a database with approximately 60,000 upper endoscopies performed in a uniform way.
Nowadays the system with the standard reports and text blocks is accepted and used in about 30% of the Dutch Hospitals.

NOTES

- Members of the TRANS.IT Project group, in alphabetical order, are: G.P. van Berge Henegouwen, M. Bruno, J.A.G. Drapers, P. Fockens, M.J.M. Groenen, G. den Hartog, G.H.J. van der Hoorn, P.J. Kingma, A.W.M. van Milligen de Wit, S.A. Mulder, P. Niermeijer, R.J.Th. Ouwendijk, P.J. van der Schaar, T. Schwartz, R. Soekhoe, W.N.H.M. Stuifbergen, A.A. Tanis, P.J. Wahab.
- Presented in part as a poster at the 10th United European Gastroenterology Week, Geneva, 2002 (*Endoscopy 2002; 34 (Suppl II) A276*).
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PHOTO QUIZ

A pregnant woman with shortness of breath

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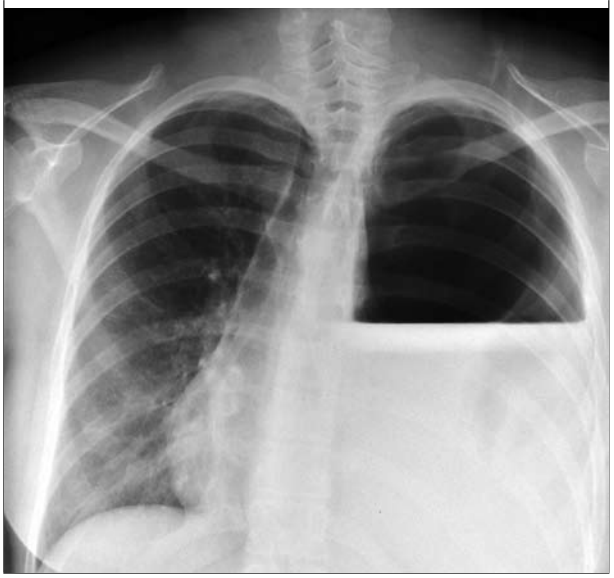
CASE REPORT

A 26-year-old woman who was five months pregnant (gravida 1, para 0) presented to the emergency department complaining progressive shortness of breath, left-sided chest pain, nausea and vomiting for the last few weeks. Eight years before, after a skiing accident, she had suffered a paralysis of the left hemidiaphragm (no rupture). Physical examination revealed absent breath sounds in the left hemithorax. The oxygen saturation was 90%. The chest radiograph is shown in *figure 1*.

WHAT IS YOUR DIAGNOSIS?

See page 95 for the answer to this photo quiz.

Figure 1. *Chest radiograph*



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CASE REPORT

Chronic-contained rupture of an infected aneurysm of the abdominal aorta due to *Listeria monocytogenes*

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ABSTRACT

We report a case of chronic-contained rupture of an infected aneurysm of the abdominal aorta, from which *Listeria monocytogenes* was cultured. The diagnosis of rupture and retroperitoneal mass was made by computed tomography, whereas FDG-PET diagnosed vessel wall inflammation. The infectious nature only became apparent at surgery.

KEYWORDS

Aortic rupture, aneurysm, diagnostic imaging, infected, listeria infections

INTRODUCTION

Infected aneurysms represent a diagnostic and therapeutic challenge. *Listeria monocytogenes* is very rarely reported as the causative organism of infected aortic aneurysm. This gram-positive bacillus has emerged as an important food-borne pathogen in the last 20 years.
We report a case of a chronic-contained rupture of an infected aneurysm of the abdominal aorta, from which *L. monocytogenes* was cultured.

CASE REPORT

Three weeks before admission to our university hospital, a 75-year-old woman was hospitalised elsewhere because of a progressively deteriorating clinical condition (characterised by anorexia and fatigue) and acute low back pain. Laboratory evaluation revealed a C-reactive protein (CRP) of 77 mg/l (normal <12), a white blood cell count (WBC) of 8.4 x 10^9/l (normal 3.5 to 11.0 x 10^9/l), and a haematocrit value of 29% (normal 37 to 47). On computed tomography (CT) of the abdomen, retroperitoneal fibrosis was suspected and she was therefore treated with methylprednisolone. The clinical state of the patient improved and she was discharged one week later, on 40 mg methylprednisolone daily. For unclear reasons, the methylprednisolone was stopped by her general practitioner.
In the following two weeks, her clinical condition deteriorated and she was referred to our hospital. Her past history revealed coronary artery disease, hypertension, hysterectomy and cholecystectomy.
On physical examination, the patient was afebrile, blood pressure was 164/82 mmHg and pulse rate 72 beats/min. A discrete aortic valve murmur was noted; lung and vascular examination was unremarkable. An extensive blood and urine analysis revealed a CRP of 18.8 mg/l (normal <5), WBC of 9 x 10^9/l (normal 4 to 9 x 10^9/l) and haematocrit 46%. A monoclonal IgG-κ gammopathy was also noted, the significance of which was not clear. Since the patient remained afebrile, no blood cultures were taken.
A positron emission tomography (PET) with radioactive labelled 18-fluoro-deoxyglucose (FDG) showed increased radiotracer uptake around the abdominal aorta (*figure 1*). A control CT of the abdomen demonstrated a saccular aneurysm of the infrarenal aorta with a hypoattenuating mass anterior of the aneurysm, suggestive of a chronic-contained rupture of an abdominal aortic aneurysm (*figure 2*). The area of increased radiotracer uptake corresponded to the area of concern on the CT scan.

The aneurysm was excised and replaced by a rifampicin-bonded Gelsoft graft with reimplantation of the right renal artery.

Figure 1. *Coronal positron emission tomography shows increased radiotracer uptake around the abdominal aorta (arrow)*

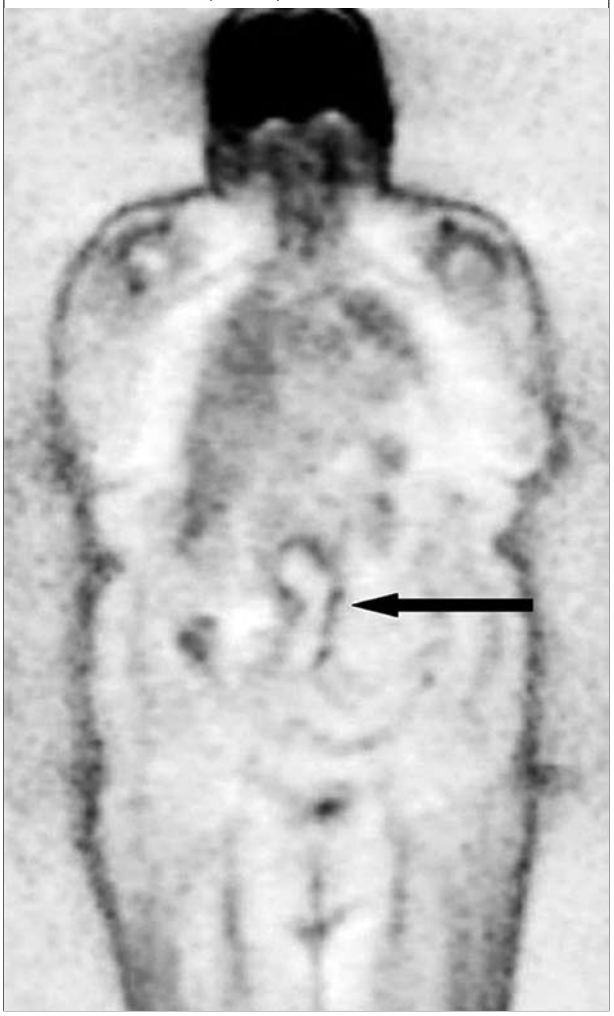
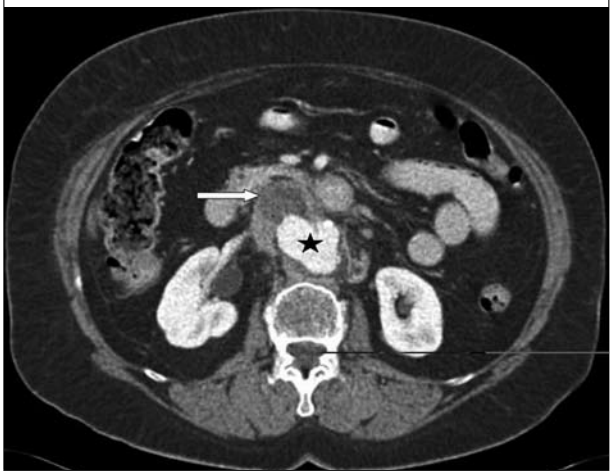


Figure 2. *Repeat transverse contrast-enhanced CT scan - performed 21 days after the first examination - shows a saccular aneurysm (★) with a hypoattenuating mass anterior of the aneurysm (arrow), corresponding to extravasation of blood*



Cultures of the resected material as well as of the haematoma yielded *Listeria monocytogenes*. Treatment was started with ampicillin 1 g every six hours. After four weeks of intravenous therapy, the patient was discharged home and the regimen was changed to oral antibiotic therapy with trimethoprim-sulphamethoxazole 800/160 mg by mouth every 12 hours for another two weeks.

DISCUSSION

Aortic infection develops when a pathogen offends a vulnerable aortic wall. It can arise following bacterial invasion of a previously normal or atherosclerotic aorta and, more commonly, through secondary infection of an existing atherosclerotic aneurysm.[1]

The organisms most frequently isolated are *Staphylococcus aureus*, *Salmonella* species and *Streptococcus* species. A trend toward the involvement of more gram-negative aerobes and anaerobes has been noted (*Clostridium, Pseudomonas, Escherichia coli*, and *Bacteroides*).[2,3]

Although a long list of additional organisms have been reported to cause infected aortic aneurysms, *L. monocytogenes* is a rarity. This food-borne, gram-positive bacillus is widespread in the environment and has been isolated from dust, numerous human (fresh and processed) food products, animal feed, water, sewage, numerous species of animals and asymptomatic humans (5% of the population are estimated to be asymptomatic faecal carriers).[4,5]

It tends to infect the very young and the elderly, pregnant women and immunosuppressed patients (due to malignancy, organ transplant, corticosteroid use or chronic diseases such as diabetes mellitus and cirrhosis).[5] In adults, meningitis or meningoencephalitis and bacteraemia are the principal forms of listeriosis.

Other clinical manifestations have been described, such as pneumonia, conjunctivitis, cholecystitis, lymphadenitis, dermatitis, endocarditis, septic arthritis, peritonitis, osteomyelitis, prosthetic joint infections, prosthetic graft infections and aortitis.[2,5-7]

The diagnosis of an infected aortic aneurysm is usually suspected on imaging studies and confirmed by culturing an organism from the blood. Blood cultures can be negative in up to 50% of the patients, though organisms can be isolated from aneurysmal tissue in up to 75%.[8]

CT scanning with contrast enhancement is the diagnostic tool of choice. Several characteristic features such as saccular shape, rapid expansion and periaortic soft-tissue mass, stranding and/or fluid in an unusual location (thoracic and abdominal aorta at or above the renal arteries) are highly suggestive of an infected aortic aneurysm.[1]

Due to its ability to demonstrate increased *in vivo* glucose consumption in areas of inflammation, an FDG-PET scan can visualise aortitis caused by vasculitides, by autoimmune phenomena, by retroperitoneal fibrosis and by infection.[9] Atherosclerotic inflammation will also cause some FDG accumulation in the vessel wall, but not to the same extent that infection or true vasculitis does.[10] FDG-PET scan, however, does not allow the differentiation between inflammatory and infectious aortitis.

In our patient, a diagnosis of retroperitoneal fibrosis was first made. Therefore, an FDG-PET scan was performed. Increased radiotracer uptake was noted, which corresponded to the area of the ruptured aneurysm present on repeat CT scan. Our patient had more widespread atherosclerosis, as calcifications of the iliac arteries on CT scan showed, but these atherosclerotic lesions did not take up FDG.

A high index of suspicion and correct interpretation of imaging findings, i.e. characteristic features on CT in combination with increased radiotracer uptake on FDG-PET, are critical for early diagnosis and treatment of infected aortic aneurysms.

The preferred treatment of listerial infection is ampicillin. In case of tolerance to ampicillin, an aminoglycoside should be added, since *in vitro* synergy has been observed. In patients with penicillin hypersensitivity, trimethoprim-sulphamethoxazole and vancomycin are the next best choices.[2,4,5] The optimal duration of antibiotic therapy is unknown; however, therapy for at least six weeks is generally recommended.

CONCLUSIONS

Infected aneurysms represent a diagnostic and therapeutic challenge. CT is considered to be the best diagnostic imaging modality in infected aortic lesions. The use of FDG-PET, which gives the opportunity to distinguish between inflammatory and noninflammatory aortic aneurysms, can make an important contribution to the diagnosis.

We believe this case represents the first description of chronic-contained rupture of an infected aneurysm due to *Listeria monocytogenes*.

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CASE REPORT

Pleural thickening in a construction worker: it is not always mesothelioma

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ABSTRACT

We describe the case of a 45-year-old man presenting with chest pain and pleural effusions. These symptoms were progressive over a period of three years, with pericardial involvement and respiratory insufficiency finally resulting in death. Despite repeated diagnostic procedures, a final diagnosis could only be made at autopsy. Multisystem foamy histiocyte infiltration suggested the diagnosis of Erdheim-Chester disease.

KEYWORDS

Chest pain, Erdheim-Chester disease, pleural effusion

INTRODUCTION

Erdheim-Chester disease (ECD) is a rare, life-threatening multisystem disease that is characterised by infiltration of foamy histiocytes.[1-3] This disease was described for the first time by Chester and his tutor Erdheim in 1930.[1] The aetiology is unknown. Bone pain is the most common presenting symptom and characteristic radiographic changes are bilateral sclerosis of the long bones, predominantly in the diaphyses and metaphyses. Approximately 50% of the patients have involvement of other tissues, such as periorbital, heart, skeletal muscles, skin and lung.[4] Allen found 176 cases,[5] among them 41 cases with pulmonary involvement. We describe the case of a middle-aged man with pulmonary involvement of ECD, but without skeletal pain.

CASE REPORT

In January 2000, a man aged 45 years first experienced chest pain and a nonproductive cough on a skiing trip. Treatment with a macrolide resulted in substantial improvement. Six months later, these symptoms recurred with increased intensity. He noticed chills and night sweats, but no fever. The symptoms worsened and he developed increasing shortness of breath on exertion. In June 2000 he could only walk about 100 meters.

Apart from a slightly raised erythrocyte sedimentation rate, there were no abnormalities in the blood biochemistry. In September 2000, chest X-rays showed bilateral pleural thickening and a decreased volume of the right lung. CT scan showed pleural thickening and subpleural fibrotic deformity, but no lymphadenopathy. Pulmonary function tests showed mild restriction and decreased static lung volumes (*table 1*). A tru-cut pleural biopsy showed fibrous tissue and chronic inflammation. He was treated for several months with ibuprofen 600 mg three to four times daily with little effect.

In October 2001 he was seen for the first time in our outpatient department. His only medical history was a nonsymptomatic diaphragmatic hernia and knee surgery. He had never smoked and had never been in contact with tuberculosis patients. He was unaware of any asbestos exposure in his job as a construction worker. On physical examination, tachypnoea was noted but no further abnormalities. A repeated CT scan showed stable disease.

Table 1. *Pulmonary function tests*

	November 2000	November 2002
Vital capacity litres (% predicted)	3.0 (62)	1.5 (40)
FEV_1 litres (% predicted)	2.5 (63)	1.3 (30)
TLC litres (% predicted)	4.5 (61)	2.9 (40)
RV litres (% predicted)	1.3 (63)	1.1 (50)

FEV_1 = forced expiratory volume in one second; TLC = total lung capacity; RV = residual volume.

There was no sign of pleural effusions and his pulmonary function tests showed a further reduction in lung volumes (*table 1*). Repeated blood biochemistry and haematology were normal. A tuberculin skin test was negative. The histology of a second tru-cut biopsy was identical to the previous one. Moreover, no infectious organisms were seen and cultures for tuberculosis, aspergillosis and actinomyces were negative.

Despite empirical therapy with up to 40 mg of prednisolone his symptoms and pulmonary function worsened. In June 2002 an open lung biopsy was performed. The pleurae were thickened to about 3 cm with a yellow discoloration and several adhesions. Biopsies showed extensive fibrosis, with infiltration of lymphocytes, plasma cells and histiocytes. A few clusters of histiocytes with foamy cytoplasm were present. No micro-organisms were identified, and there was no evidence of a malignant tumour. Six months after the open lung biopsy, there was further clinical deterioration, and signs and symptoms of right-sided heart failure and respiratory insufficiency developed. He was admitted to the ICU for mechanical ventilation. CT scan showed extensive pleural and pericardial thickening and effusions, diffuse smooth interlobular septal thickening and patchy areas of ground-glass attenuation (*figure 1*). There were no centrilobular abnormalities. The extent of the abnormalities prohibited decortication. High-dose corticosteroids were started as well as cyclophosphamide and broad-spectrum antibiotics.

After a few days he was successfully extubated, but his right-sided heart failure recurred the next day. A cardiac ultrasound showed pericardial effusion without inflow disruption. A pericardectomy was considered but rejected on account of the lack of a diagnosis and treatment options. Shortly thereafter, the patient died and autopsy was performed. At autopsy, the pleura were fibrotic with abundant infiltration of foamy histiocytes. Multinucleated cells were also present (*figure 2*). The fibrosis and histiocytic infiltration extended into the lung. Foamy histiocytes were found in the retroperitoneum, mesentery, spleen and bone marrow. These findings are consistent with ECD.

Figure 1. *CT scan showing extensive pleural and pericardial thickening and effusions, diffuse smooth interlobular septal thickening and patchy areas of ground-glass attenuation, with no centrilobular abnormalities*

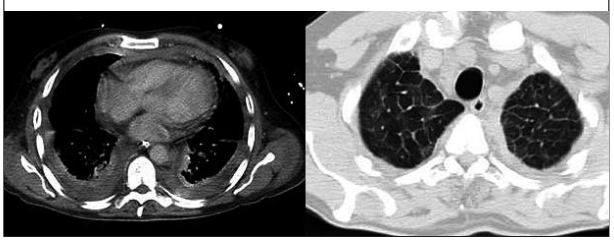
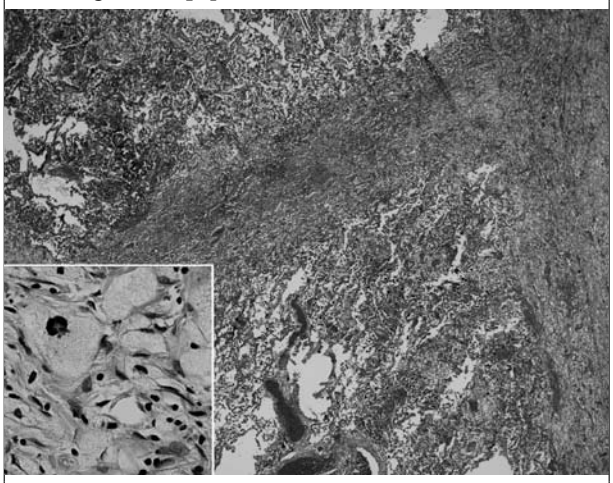


Figure 2. *Haematoxylin and eosin stained section of the lung at autopsy*



Extensive fibrosis of the pleura and interlobular septa. Inset: Higher magnification showing infiltrate with foamy histiocytes and some multinucleated histiocytes.

DISCUSSION

ECD primarily affects middle-aged and older adults. Since the histiocytic infiltration is mainly found in the large bones of the extremities, the most common presentation is with bone pain. Radiographic examination of the long bones shows characteristic changes: a symmetric pattern of diffuse or patchy sclerosis in the diaphyses and metaphyses of the long bones, a coarsened trabecular pattern and cortical thickening.[6-8] These skeletal abnormalities often result in only mild symptoms. Extraskeletal manifestations are present in half of patients and are the main determinants of survival. With pulmonary involvement, the morbidity and mortality increase substantially.[5,9] Pulmonary ECD typically presents with dyspnoea and a nonproductive cough. Pulmonary function tests show a mild restrictive defect and a decrease in carbon monoxide transfer. Gas exchange stays normal until the very final stages of the disease.[10-12] On chest CT scan, the most common findings are smooth interlobular septal thickening and centrilobular nodular opacities, visceral thickening and pleural effusions. The pericardium is frequently involved with thickening and fluid effusions.[13] Histopathologically, lung involvement is characterised by accumulation of foamy or clear histiocytes, variable amounts of associated fibrosis, and variable lymphoplasmacytic inflammatory infiltrates arranged in a lymphangitic pattern.[2,3,14]

There is no evidence-based treatment for ECD. Recently, disease stabilisation was reported by using prednisolone 40 mg in combination with cyclophosphamide 100 mg once daily.[15] Treatments with various other agents have been reported, such as vinblastine, vincristine, adriamycin,

colchicine and radiotherapy, in various combinations, but with only minor effects.[2,3,9] Braiteh *et al.* reported successful treatment with interferon-α.[16]

Our patient presented with only pulmonary symptoms. Since he did not complain of bone pain, the diagnosis of ECD was not considered. Rather, a presumptive diagnosis of mesothelioma was made based on the combination of extensive pleural thickening, a restrictive pulmonary function defect and the fact that our patient was a construction worker. Unfortunately, a clear diagnosis could not be made on the tissue samples obtained during surgery. Because the histological findings of fibrosis, chronic inflammation and some foamy histiocytes are nonspecific, a tentative diagnosis of ECD can only be made if clinical data, radiological findings and pathological findings are considered together. The most reliable diagnostic procedure is reported to be radiological investigation of the tubular long bones.

In our patient, the disease took a much more aggressive course after surgery, with extensive pulmonary involvement on top of the pre-existent pleural abnormalities. An infectious contribution was excluded by microbiological bronchoalveolar lavage. Repeated tissue sampling was refused by the patient. Empirical treatment with steroids and cyclophosphamide was followed by a very short improvement but might have been more successful if instituted at an earlier stage.

In conclusion, ECD should be included in the differential diagnosis of bilateral pleural thickening and a restrictive pulmonary impairment. The disease has a poor prognosis and limited treatment results have been reported with prednisolone and cyclophosphamide.

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CASE REPORT

Recalcitrant leg ulcer due to mixed connective tissue disease

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ABSTRACT

We present a 28-year-old woman with mixed connective tissue disease (MCTD) complicated by a recalcitrant longstanding leg ulcer, which responded to complex therapy with local polydine, systemic ciprofloxacin, iloprost, enoxaparin and aspirin. Cyclophosphamide pulse therapy and corticosteroids controlled the systemic inflammation but failed to heal the leg ulcer. We considered a rationale of complex therapy for the leg ulcer on a basis of pathogenesis and complications of MCTD.

KEYWORDS

Ciprofloxacin, enoxaparin, iloprost, mixed connective tissue disease, recalcitrant leg ulcer

INTRODUCTION

Mixed connective tissue disease (MCTD) is an overlap syndrome combining features of systemic lupus erythromatosus, rheumatoid arthritis, systemic sclerosis and polymyositis, together with the presence of antibodies to U1-RNP.[1] Analysis by immunoblotting showed that the major epitopes recognised by MCTD sera are a 68kDa polypeptide bound to U1 (uridine-rich)-RNA. Skin manifestations of MCTD include Raynaud's phenomenon associated with oedema of the hands, sclerodactyly, calcinosis, telangiectasia, photosensitivity, malar rash and the rash of dermatomyositis. Chronic leg ulcers are not rare in MCTD or overlap syndromes. We describe a patient with MCTD who developed a chronic refractory leg ulcer, which responded to complex therapy.

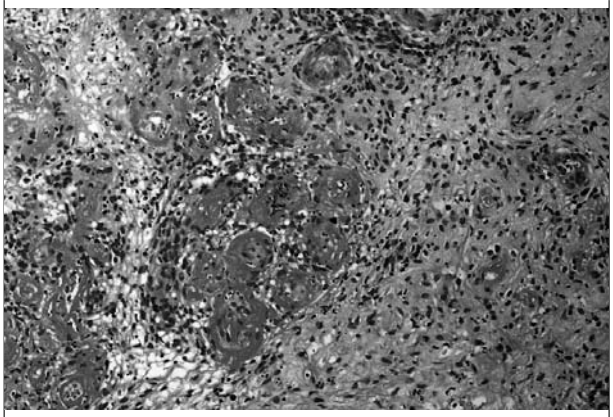
CASE REPORT

A 28-year-old woman developed fever, symmetric painful swelling of the hands, Raynaud's syndrome, teleangiectasia, livedo reticularis, polyarthritis and oesophageal dysmotility in 1998. Heart, lungs and kidneys were intact. At that time she was leucopenic (3600/mm^3), anaemic (haemoglobin 9.7 g/dl) with a positive Coombs test and an elevated erythrocyte sedimentation rate (80/h). Immunological analysis showed a high titre of speckle pattern antinuclear factor, positive anti-DNA and anticardiolipin antibodies, negative lupus anticoagulant, positive SS-A/Ro antigen, negative SS-B/La antigen, Smith antigen, antitopoisomerase, anticentromere antibodies, borderline low C3-C4, high serum level of rheumatoid factor (1000 IU/ml) and ribonucleoprotein at haemagglutination titre of 1:1600, and polyclonal hypergammaglobulinaemia. Tests for antineutrophil cytoplasmic antibodies, and cryoglobulins were negative. Hepatitis-B surface antigen and hepatitis-C virus were negative. Bone marrow showed nonspecific reactive changes. Gastrointestinal endoscopy, total body CT and bone scan were normal. Coagulation testing showed no mutations of prothrombin, methyltetrahydrofolate reductase, and Leiden V factor. Antithrombin III, protein C and S activity, protein C resistance, prothrombin time, international normalised ratio and partial thromboplastin time were normal. An increased level of fibrinogen (488 mg/dl, normal 160 to 400), borderline low thrombin time and a high level of factor VIII (256%, normal 55 to 150) with elevated D-dimers (2.17 mg/l, normal <0.5) were found. Echocardiography was normal except for borderline pulmonary artery pressure (30 mmHg). The clinical and laboratory findings were consistent with mixed connective tissue disease (Alarcon-Segovia and Villanreal criteria). Initially she responded to corticosteroid, hydroxychloroquine and methotrexate therapy. Two years later, the methotrexate was stopped

because of recurrent episodes of fever, and respiratory and urinary tract infections. She needed moderate to high doses of prednisone (20 to 40 mg/day) to control the fever, polyarthritis and neutropenia. In 2001 the patient developed a small skin ulcer on the right ankle. The ulcer extended despite multiple local therapies: chlorhexidine gluconate 0.5% irrigation, topical antibiotic and steroid ointments, hydrocolloid gel and dressing, calcium-sodium alginate fibres and Becaplermin gel 0.01%. Ultrasound Doppler of the leg vessels and ankle-brachial index were normal. Repeated marginal biopsies did not show vasculitis, pyoderma gangrenosum, or malignancy, but only nonspecific inflammation. Her general condition was still poor with sustained fever and active polyarthritis. The dose of prednisone was raised to 40 mg/day; the fever and synovitis resolved but she developed vertebral osteoporotic fractures. Azathioprine was added to the hydroxychloroquine and corticosteroid therapy. Four months later she developed sepsis with multiple abscesses of the abdomen and respiratory failure due to massive pneumonia resulting from severe leucopenia (1800/mm^3); the azathioprine treatment was stopped. The patient was critically ill, and needed long-term intensive therapy. She was treated with respiratory support, intravenous antibiotics, abscess incisions, intravenous immunoglobulins and parenteral corticosteroids. The infectious complications were cured, but her leg ulcer continued to expand and achieved 3.5 cm in diameter (*figure 1*). Episodes of fever, arthritis and cytopenia recurred requiring treatment with moderate doses of steroids. In the interim another marginal biopsy showed leucocytoclastic vasculitis and intimal small-vessel proliferation with thrombi (*figure 2*). At this point cyclophosphamide monthly pulse infusions (1 g) were started. Cyclophosphamide therapy reduced disease activity; the fever, haemoglobin and white blood cell count returned to normal, the arthritis remitted and the prednisone dose was reduced to 5 mg/day. However, the leg ulcer remained unchanged (*figure 1*). We decided to begin complex inpatient therapy. This therapy (known as the acronym AAVAA) included:

1) Antiseptic therapy consisting of local povidone iodine soap cleanser (0.75% iodine) for leg baths twice a day, each procedure lasting 30 minutes, with further iodine 1% dressing until complete wound healing.

Figure 2. *A biopsy obtained from the ulcer edge of the patient with MCTD*



In the deep dermis there are extensive fibrin deposits in the small blood vessel walls with intimal proliferation along with neutrophils and fibrin thrombi, which plug the blood vessels' lumina. (Haematoxylin-eosin X 400).

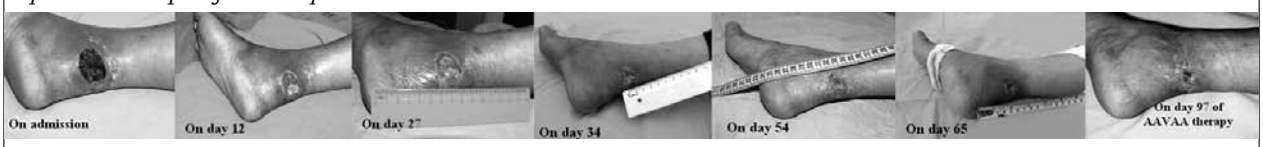
2) Antibiotic treatment with intravenous amoxycillin+ clavulenic acid according to ulcer flora susceptibility followed by oral ciprofloxacin 500 mg twice daily until complete wound healing.
3) Vasodilatatory/vasomodulatory therapy with long-term infusion of the prostacyclin analogue ilomedin (iloprost thromethamine) (Agis) for seven weeks.
4) Anticoagulant therapy with low-molecular-weight heparin enoxaparin: clexane (Aventis Pharma) 40 mg/day subcutaneous for two months.
5) Antiaggregant therapy with aspirin 100 mg/day.

AAVAA therapy brought about complete healing of the ulcer leg (*figure 1*) after three months, which had been refractory to therapies for three years. The characteristic dynamics of wound contraction were followed (*figure 3*). No systemic, local or scar complications were observed during and after AAVAA therapy.

DISCUSSION

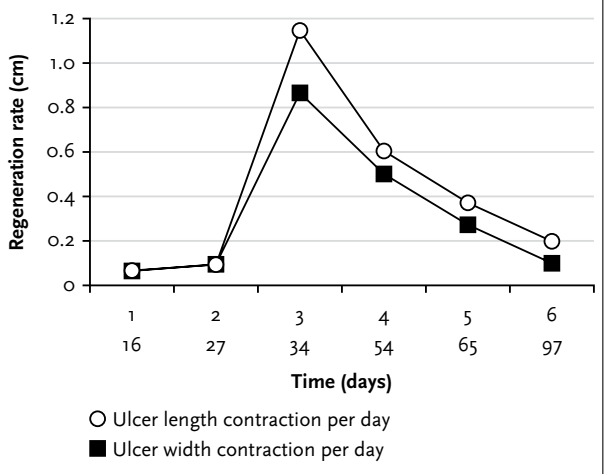
Vascular, infectious and tumour-associated causes, pyoderma gangrenosum and pressure sores must be

Figure 1. *Large leg ulcer (3.5 x 2.5 cm) associated with MCTD that had been refractory to multiple local and systemic therapies for three years*



Complex antiseptic, antibiotic, vasodilatatory, anticoagulant and antiaggregant (AAVAA) therapy was administered and achieved complete relief of the inflammation and ulcer healing in three months.

Figure 3. *Three periods of ulcer healing during AAVAA therapy*



The first one (27 days) was of very slow regeneration and associated with treatment of the affecting factors interfering with normal regeneration: infection, inflammation, vascular damage and thrombosis. The second period (27-54 days) was associated with rapid wound regeneration with a peak on the 34th day, which was followed by the third period (54-97 days) of slower healing due to the phenomenon of contact cell inhibition. Regeneration rate = contraction of the wound length/day and the wound width/day.

considered in patients with cutaneous ulceration and autoimmune disease. Ulcerations secondary to ischaemia may result from vasospasm (Raynaud's phenomenon), vascular thrombosis (antiphospholipid syndrome or paraproteinaemia) and vascular necrosis (necrotising venulitis or arteritis). Besides malignancy with typical morphology and histology all the above-mentioned influences might be involved in the aetiology of the leg ulcer in our patient.

The image of MCTD as a benign rheumatic disease with a favourable response to therapy is currently under revision. Serious vascular disease with thrombotic complications, pulmonary hypertension and heart failure are common and result in significant morbidity and mortality.[2] We observed a rare form of severe vascular disease due to MCTD complicated by a recalcitrant leg ulcer, which only responded to complex therapy. The rationale for this complex therapy for the leg ulcer was as follows.

The need to treat local infection with effective local and systemic antibiotic long-term therapy according to microbial susceptibility up to complete wound healing,

Wound infection might be responsible for the unhealed ulcer and be an origin for microbial dissemination through this 'open gate'.

Microvascular impairments of MCTD with intimal proliferation, medial hypertrophy, affecting small and medium-sized vessels with occlusion[3] and hypercoagulation abnormalities (D-dimers, high factor VIII, elevated fibrinogen, anticardiolipin antibodies) found in our patient justified therapy with anticoagulant enoxaparin, aspirin and iloprost. An angiographic study reported a high prevalence of medium-sized vessel occlusions in patients with MCTD.[4] The anticoagulant therapy has been reported to be beneficial in MCTD associated with arterial thrombosis,[5] pulmonary hypertension,[6] Budd-Chiari syndrome[7] and acute right cardiac failure due to pulmonary thromboembolism.[8] For the first time we report effective anticoagulant (enoxaparin), aspirin and iloprost therapy for MCTD complicated by a recalcitrant leg ulcer.

A number of double-blind placebo-controlled studies of iloprost infusion given intravenously have shown benefit in Raynaud's syndrome.[9,10] In addition to its vasodilatory and antiplatelet effects, iloprost has been shown to downregulate lymphocyte adhesion to the endothelium.[11] When compared with nifedipine, it was found to have the same effect on reducing the frequency of the vasospastic attacks, but was more effective in healing digital ulcers and appeared to produce fewer adverse effects. Iloprost is the first choice for patients with critical ischaemia or ulceration. It can produce benefit lasting for between six weeks and six months in most patients.

The necessary prerequisite of successful treatment was immunosuppressive therapy for vasculitis with cyclophosphamide pulses, corticosteroids and hydroxychloroquine; however, although this therapy controlled the systemic disease, it did not result in wound healing. Besides its antibiotic properties, ciprofloxacin was reported as an activator of interleukin-3 production, granulocyte-macrophage colony-stimulating factor and haemopoesis,[12-15] which are important for wound healing, and as inhibitor of antiphospholipid antibodies.[16] A high dose of ciprofloxacin has been reported to inhibit tumour necrosis factor-α production, lymphocyte blast transformation and synthesis of immunoglobulins.[17,18] By understanding the mechanisms that act to delay healing, chronic wound healing becomes a true science rather than a clinical art.[19]

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ANSWER TO PHOTO QUIZ (ON PAGE 84)

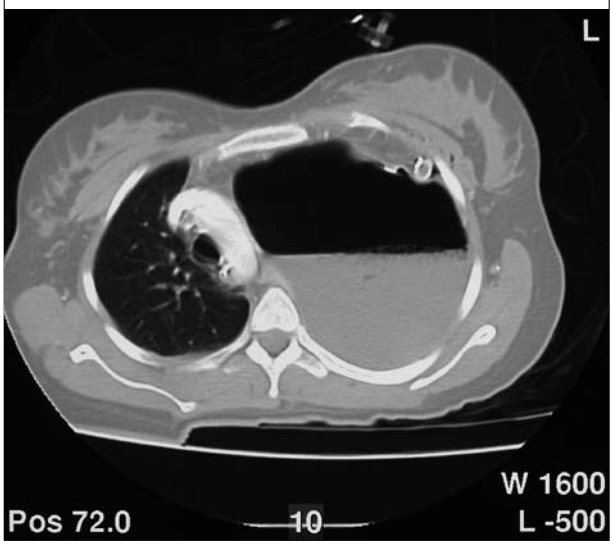
A PREGNANT WOMAN WITH SHORTNESS OF BREATH

DIAGNOSIS

The chest radiograph was interpreted as showing a left pneumothorax with pleural fluid, so a chest tube was placed (2nd intercostal space ventrally). After insertion the tube returned air and (later) scant yellow fluid. Biochemical investigation of this fluid showed a pH of 3.3. A chest CT scan performed immediately thereafter showed a ruptured left hemidiaphragm with an intrathoracic stomach and bowel (*figure 2*). An urgent laparotomy was carried out. On operation, an enormously dilated stomach, part of the intestine, colon and the spleen had herniated into the thorax. The collapsed left lung was small and pale. The ruptured diaphragm and perforated stomach were repaired. After surgery, the lung re-expanded and the patient recovered uneventfully.

Diagnosis: diaphragm rupture with intrathoracic stomach.

Figure 2. *Chest CT scan showing a dilated intrathoracic stomach*



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2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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