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Contents

Cover
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for details see page 147

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EDITORIAL

Are the effects of local treatment with glucocorticoids only local?

S.A.C. VAN TUYL AND P.H.TH.J. SLEE

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Glucocorticoids can be applied locally in several ways: by inhalation, intranasally, transdermally, by intra-articular injection, by enema or intraspinally. Most literature on unwanted side effects stems from inhalation of glucocorticoids.[1] However, clinicians should be aware that although rare, side effects are possible with all local applications of glucocorticoids. Systemic and unwanted effects are related to the glucocorticoid activity of the drug, the dose and duration of the glucocorticoid treatment, but also depend on the systemic absorption or bioavailability of the corticosteroid and possibly on individual sensitivity to glucocorticoids as well.

In this issue of the Journal two articles expound on two unwanted systemic effects of locally administered glucocorticoids. One article is about iatrogenic hypercortisolism, which is the most frequent cause of Cushing's syndrome, and the other is on suppression of the hypothalamic-pituitary-adrenal (HPA) axis, which might place patients at risk of developing stress-induced acute adrenal insufficiency, especially after withdrawal of the corticosteroid.

Abma and colleagues describe a patient who developed Cushing's syndrome after three years of transdermal steroid treatment. The patient presented with complaints of fatigability, increased body weight and a Cushingoid appearance.[2] The plasma cortisol concentration of the patient – which gives no information on the presence of clobetasol propionate – was very low. This supports the diagnosis of iatrogenic Cushing's syndrome and concomitant adrenal suppression. The transdermal application was withdrawn during a period of two weeks and glucocorticoids were substituted. When the patient suffered from a urinary tract infection, she developed a symptomatic adrenal insufficiency, as she was on an apparently suboptimal replacement glucocorticoid dose.

Jansen and Van Roon describe four patients who developed Cushing's syndrome after only one or two intra-articular injections of triamcinolone acetonide.[3] According to the literature, such a normal dose of triamcinolone acetonide rarely causes any side effects.[4] The authors only gave data on plasma cortisol and ACTH in one patient. Two months after the injection, ACTH was not detectable and cortisol levels were very low. The comments of the authors focus on Cushing's syndrome, whereas adrenal suppression was also evident.
They claim a clinical difference in two different triamcinolone preparations: triamcinolone acetonide and triamcinolone hexacetonide. The differences in pharmacokinetic properties of these two triamcinolone preparations have been studied.[5] After a single intra-articular injection of triamcinolone acetonide and triamcinolone hexacetonide in different doses, plasma concentrations of these steroids were detected for two to three weeks. Both preparations were completely absorbed but the release of triamcinolone hexacetonide was significantly slower, probably because of the lower solubility. The level of systemic triamcinolone correlated with the suppression of endogenous cortisol, which was present during the first week.[5] According to Caldwell *et al.* there is no evidence of clinically significant adrenal insufficiency after intra-articular injections, but we know of at least one article on an acute adrenal crisis in a patient treated with two intra-articular steroid injections.[6,7] What approach should a clinician take if these side effects occur? If suppression of the HPA axis is suspected, the

first step is to determine the basal cortisol concentration at 9 a.m. A cortisol concentration less than 100 nmol/l is strongly associated with adrenal dysfunction. If the basal plasma cortisol concentration is more than 100 nmol/l a stimulation test is needed to find out whether the adrenal response is suppressed.[8] Traditionally, the function of the HPA axis is tested using the insulin tolerance test (ITT) and the metyrapon test. However, both tests are not only inconvenient for the patient and impractical, but also potentially dangerous. The CRH (cortisol-releasing hormone) test is expensive and has a low sensitivity and specificity.[9] A low-dose ACTH test (1 μg instead of 250 μg i.v.) has been reported to be highly sensitive and specific for diagnosing adrenal suppression.[10] When suppression of the HPA axis is suspected, it is important to instruct the patient to come to the hospital in situations which provoke adrenal insufficiency.

Is there an explanation for this difference in individual sensitivity to corticosteroids? Whereas decreased sensitivity to the corticosteroid receptor is described more frequently in the literature, Iida and colleagues first described increased sensitivity to the glucocorticoid receptor in 1990.[11] The patient had clinical characteristics of Cushing's syndrome and low cortisol concentrations on several occasions. Exogenous corticosteroids were the best explanation for the clinical picture and laboratory abnormalities, but this could not be confirmed. The authors therefore considered a cortisol hyperreactive syndrome. *In vitro* experiments with the patient's skin fibroblasts supported the concept of an increased sensitivity to glucocorticoids. More recently, Huizenga and colleagues described a polymorphism in the glucocorticoid receptor that was associated with increased receptor sensitivity. In this study, 13 patients carrying a mutation in the glucocorticoid receptor (N363S carriers) were identified. The patients with this mutation had a significantly higher body mass index (BMI) and there was a trend towards a lower bone mineral density, which suggests that they are more sensitive to the effects of glucocorticoids. A low-dose dexamethasone suppression test, using 0.25 mg instead of 1 mg dexamethasone, demonstrated significantly larger cortisol suppression in the N363S carriers.[12] Furthermore, Newfield and colleagues have described a girl who developed Cushingoid features in prepuberty in the presence of normal cortisol levels and who was earlier reported to have markedly elevated glucocorticoid receptor sites per peripheral lymphocyte with normal binding affinity as a potential cause of her phenotype.[13] We reported on a patient who received two intra-articular triamcinolone acetonide injections. She developed the clinical characteristics of Cushing's syndrome and had an asymptomatic adrenal insufficiency, which resolved after six months. A dexamethasone suppression test, using 0.25 mg instead of 1 mg dexamethasone, demonstrated a significant decrease in the morning cortisol. The response of peripheral blood mononuclear cells to dexamethasone in a mitogen-stimulated proliferation assay in this patient showed a lower IC50 than normal controls, supporting the diagnosis of increased glucocorticoid sensitivity.[14] Personal communication: J.W. Koper.
There are still questions to be answered. Is there a direct relationship between the induction of Cushing's syndrome and adrenal suppression? Is it possible to recognise patients at risk for suppression of the HPA axis?
It is important to realise that although local administration of glucocorticoids is generally considered to be safe, it can sometimes cause serious side effects. It is still unclear why some patients develop Cushing's syndrome and long-lasting adrenal suppression. It is possibly influenced by a variable glucocorticoid sensitivity of the receptor. So far we are not able to identify patients who are at risk of developing adrenal insufficiency after local glucocorticoid administration. Until then, we can only bear it in mind and keep our patients alert.

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REVIEW

Primary pulmonary hypertension

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INTRODUCTION

Primary pulmonary hypertension (PPH) is characterised by sustained elevations of pulmonary arterial pressure without an apparent cause. Normal mean pulmonary arterial pressure lies between 12-16 mmHg. The National Institutes of Health (NIH) registry defines pulmonary hypertension as the presence of a mean pulmonary arterial pressure of more than 25 mmHg at rest or more than 30 mmHg during exercise and by exclusion of secondary causes of pulmonary hypertension,[1] such as left-sided cardiac valvular disease, myocardial infarction, congenital heart disease including septal defects, connective tissue disease, chronic thromboembolic disease and severe chronic obstructive pulmonary disease. In several other diseases, such as portal hypertension,[2-4] human immunodeficiency virus infection,[5-7] and use of appetite-suppressant drugs (e.g. aminorex fumarate and (dex)fenfluramine)[8-10] pathological features similar to those of PPH are observed. Pregnancy, oral-contraceptive use, and cocaine are also reported to be associated with PPH.[11-13] In 1981 the use of contaminated rapeseed oil in Spain resulted in pulmonary hypertension, clinically and pathologically identical to PPH, in 20% of the affected patients.[14] Recently, Hoeper *et al.* described the occurrence of PPH four to 34 years after splenectomy.[15]

INCIDENCE

PPH is a rare disease with an estimated incidence of one to two cases per million people in the general population per year.[10,16,17] Autopsy studies have shown a prevalence of 0.13%; in patients with hepatic cirrhosis the prevalence of PPH is 0.73%.[2] The absolute risk for obese persons who have taken anorexic drugs for more than three months is more than 30 times higher than for non-users.[10]
PPH can occur at any age (even in childhood) but the highest prevalence occurs in the third and fourth decade, with a mean age at diagnosis of 36 years.[1,18,19] In one study there was a tendency towards a slightly higher mean age at diagnosis in men. PPH occurs more often in women, the female-to-male ratio ranging from 1.7:1 to 3.06:1.[1,20] The prevalence in black and Hispanic people is similar to that in the general population, but in black people a greater female-to-male ratio of 4.3:1 has been noticed.[1] A familial form of PPH is also known and accounts for 6% of the cases.[1,21] It is inherited as an autosomal dominant trait with a highly variable penetrance among families and is associated with genetic anticipation.[21,22] Genetic anticipation means that the disease occurs at younger ages and with increased severity in succeeding generations.

GENETICS

Recently, much research has been done on the molecular mechanisms of PPH. This succeeded in the localisation of the gene for familial PPH to chromosome 2q31-32.[23] Within this chromosome region germline mutations were identified in the bone morphogenetic protein receptor II gene (BMPR2).[24] Bone morphogenetic proteins are members of the transforming growth factor β (TGF-β) superfamily of circulating proteins that regulate growth and repair tissue in all organs, and the normal function of BMPR2 in the pulmonary circulation may be antiproliferative.[25,26]

It is probable that in many cases of PPH, both sporadic and familial, the disease is caused primarily by a defect in BMPR2,[25,27] although a heterozygous germline mutation in BMPR2 alone is insufficient to cause PPH.[27] A so-called second somatic genetic hit, such as mutations in TGF-β receptor and/or Bax, may be required to cause PPH.[29] The clinical and pathological features, as well as survival after onset of symptoms, are the same as in non-familial PPH.

HISTOPATHOLOGY

Historically, three histopathological patterns were described in patients with PPH. In recent years pulmonary capillary haemangiomatosis was added as a distinct entity.[30,31] The three historical histopathological patterns were plexogenic pulmonary arteriopathy, thrombotic pulmonary arteriopathy, and pulmonary veno-occlusive disease.[18] Pietra *et al.* divided primary pulmonary arteriopathy into five subsets according to the dominant structural abnormalities involving the arterial wall and lumen.[30] See *table 1* for their primary pulmonary vascular disease classification.

As plexiform lesions are a reflection of severe hypertension, some subtypes of primary pulmonary arteriopathy may represent cases that were biopsied before plexiform lesions developed. Besides, these plexiform lesions are often focal and patchy, and therefore may be missed in a particular biopsy. For these reasons Katzenstein divided PPH in four entities, see *table 2*.[32]

Table 1
Primary pulmonary vascular disease classification[30]

Primary pulmonary arteriopathy
- plexiform lesions with or without thrombotic lesions
- thrombotic lesions
- isolated medial hypertrophy
- intimal fibrosis and medial hypertrophy
- isolated arteritis
Pulmonary veno-occlusive disease
Pulmonary capillary haemangiomatosis

Table 2
Primary pulmonary hypertension entities[32]

Primary plexiform arteriopathy
Thrombotic arteriopathy
Pulmonary veno-occlusive disease
Capillary haemangiomatosis

Plexogenic pulmonary arteriopathy is characterised by an increase of smooth muscle cells of the arterial vascular tree resulting in medial hypertrophy and expansion of the muscular layer to the originally medialess arterioles leading to a so-called muscularisation of these arterioles, and finally intimal fibrosis resulting in obliteration of the vascular lumen.[33] A common finding is evidence of thrombosis in small arteries. However, these thrombi are considered secondary phenomena.[32] The plexogenic form occurs in 28 to 80% of cases of PPH.[34,35] Thrombotic arteriopathy occurs in 40 to 56% of PPH patients, and is characterised by eccentric intimal fibrosis and evidence of recanalised in-situ thrombosis.[20,35] There is widespread small vessel thrombosis combined with the changes of moderate pulmonary hypertension (medial hypertrophy, muscularisation, intimal proliferation).[36] Veno-occlusive disease occurs in less than 7 to 16% of PPH patients and is characterised by intimal proliferation and fibrosis of the intrapulmonary veins and venules.[18,20,35] Capillary haemangiomatosis is characterised by a proliferation of thin-walled capillary-sized vascular channels within the interstitium, resulting in hypertension by surrounding and compressing intrapulmonary venules.[37]

The underlying pathogenetic mechanisms of PPH are not fully understood. Several underlying mechanisms have been suggested. Generally, individual (probably genetic) susceptibility is assumed[18,20,31] with a variety of stimuli leading to identical patterns of vascular injury and repair (pulmonary vascular remodelling), and hence to pulmonary hypertension.
Vasoconstriction and proliferation of smooth muscle cells of the pulmonary arteries are prominent features in the pathogenesis of PPH. Endothelial cells probably play an important part in the remodelling process.[20,31,34,38-41] Mutations in TGF-β receptor may lead to monoclonal endothelial cell proliferation,[29] and deregulated growth of endothelial cells results in plexiform lesions.[34] The possible role of endothelial cells in the pathogenesis of PPH raises the intriguing question whether PPH is an isolated pulmonary disease or part of a more systemic disease. Up till now there is no direct evidence that such may be the case.
Vasoactive mediators probably also play an important part in pulmonary hypertension.[20,39,42,43] Endothelial cell injury causing an imbalance between vasodilators (nitric oxide, prostacyclin) and vasoconstrictors (endothelin-1, thromboxane) may lead to vasoconstriction and medial hypertrophy. The pulmonary circulation is a major site for the production and clearance of endothelin, a potent vasoconstrictor and smooth muscle mitogen, and activation of the endothelin system is associated with pulmonary hypertension.[39,44] Endothelin A receptors are found in pulmonary smooth muscle cells and mediate smooth muscle contraction and the proliferation of smooth muscle cells and fibroblasts

whereas, endothelin B receptors are located both in endothelial cells and on smooth muscle cells mediating vasoreactivity, contributing to increase in vascular tone and pulmonary vascular hypertrophy.[39,44-46]
Serotonin, a pulmonary vasoconstrictor that promotes vascular growth, is elevated in patients with PPH.[47] This may explain why fenfluramine and dexfenfluramine,[2] being serotonin reuptake inhibitors, may trigger PPH in susceptible people.
Alpha-adrenoreceptors may also play their role in the pathogenesis of PPH.[42] Alpha- and β-adrenoreceptors help to regulate pulmonary vascular tone by producing vasoconstriction or vasodilation, respectively.[48]
Intracellular calcium is another important regulator of smooth muscle contraction and proliferation.[20,42,49] Stimulation of α-adrenoreceptors increases intracellular free calcium, and therefore vasoconstriction. Potassium-ion channels also play an important part in the determination of intracellular free calcium concentration. In patients with PPH, potassium-ion channels may be blocked by the stimulation of α-adrenoreceptors,[50] or may be dysfunctional,[49] leading to an increase of intracellular Ca^{2+} with resulting vasoconstriction.

NATURAL HISTORY

Generally, patients with PPH have a poor prognosis. In the Netherlands, median survival after the first visit to the general practitioner with signs and/or symptoms that retrospectively prove to be caused by PPH is 4.6 years, while median survival after diagnosis is 2.8 years. Earlier studies showed survival rates in a similar range.[19,51] In some cases patients survive for much longer, while spontaneous regressions also occur.[52-54] Patients who responded to short-term vasodilatation with calcium-channel blockers and were subsequently treated with these agents have an improved survival,[55] as have patients treated with long-term intravenous epoprostenol.[56] Quality of life in these patients is maintained or improved. Prognostic factors are unequivocal in the literature, but cardiac index is often used as a prognostic factor.

CLINICAL CONSIDERATIONS OF PULMONARY HYPERTENSION

Pulmonary hypertension is usually classified as primary or secondary. Because the underlying pathological abnormalities may be similar, the World Health Organisation (WHO) proposed a new classification in 1998.[57]
Pulmonary hypertension is classified into five main categories, which subsequently were subdivided into subclasses. In *table 3* you will find the main categories.

Table 3
WHO's classification of pulmonary hypertension

Pulmonary arterial hypertension (primary pulmonary hypertension is classified under this category)
Pulmonary venous hypertension
Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia
Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Pulmonary hypertension due to disorders affecting the pulmonary vasculature

DIAGNOSIS

Sporadic primary pulmonary hypertension is an elusive disease to diagnose. The non-specific clinical presentation, together with the low prevalence, makes PPH difficult to diagnose and leads to a considerable patient and doctor delay. Most common presenting symptoms are dyspnoea and fatigue,[1,16,31] while other common signs include (near) syncope, chest pain, palpitations, and peripheral oedema. Physical examination shows signs of right heart failure, such as increase in the pulmonic component of the second heart sound (P_2), right-sided third and/or fourth heart sounds, and tricuspid regurgitation. In advanced disease pulmonic insufficiency, peripheral cyanosis, and oedema are observed.[1,16,18,19,31] Raynaud's phenomenon occurs in about 10% of the patients, mainly in women.[1] Tests for antinuclear antibody, antineutrophilic cytoplasmatic antibody, rheumatoid factor, human immunodeficiency virus and liver function are performed to exclude secondary causes of pulmonary hypertension, although antinuclear antibodies, mostly in low titre, may be found without evidence of connective tissue disease.[1,16,19,20] Recently, Voelkel *et al.* showed a positive correlation between elevated serum uric acid and the degree of right atrial pressure elevation.[58] Chest radiographs show increased cardiothoracic index, prominence of the main pulmonary arteries, enlarged hilar vessels, and decreased peripheral pulmonary vessels. However, 6% of patients have normal chest radiographs.[1,19]
Electrocardiographs commonly show signs of right heart strain, such as right axis deviation, right ventricular hypertrophy, and right ventricular strain.[1,19,59] Transthoracic echocardiography is a valuable tool in the diagnosis of pulmonary hypertension.[59] It shows a dilated right heart or right ventricular hypertrophy with a decrease in the ratio of acceleration to ejection time or an increase in tricuspid regurgitant wave velocity. Transthoracic or transoesophageal echocardiography is also an important diagnostic test to exclude any left-to-right shunts. Perfusion scans can either be normal or abnormal, mostly showing diffuse patchy patterns consistent with

vascular obstruction. The ventilation scan is normal.[1,16,59] Pulmonary angiography may be needed to exclude pulmonary embolism as a cause of pulmonary hypertension. Definitive assessment of PPH has to be performed by right heart catheterisation: increased mean pulmonary artery pressure, elevated right atrial pressure, normal capillary wedge pressure, and mildly reduced cardiac index are the diagnostic indices.[1] With this technique intracardiac shunting should be excluded.[20,31] When right heart catheterisation is performed, measurement of vasodilator responsiveness is mandatory, because an appropriate haemodynamic response with a fall in pulmonary artery pressure and a subsequent rise in cardiac output has a better prognosis.[59] Pulmonary function in patients with PPH generally shows a mild restrictive lung function pattern without airway obstruction.[1,18,19] Hypoxaemia and hypocapnia are usually present.[1,19,20] Diffusion capacity is generally reduced to about 70% of predicted.[1,60,61] Cardiopulmonary exercise, by way of a six-minute walking test, shows an inverse correlation with haemodynamic parameters and seems to be an independent predictor of survival.[56] Incremental cycle ergometry, in combination with additional physiological measurements, can help to distinguish PPH from primary heart disease. In patients with pulmonary hypertension $P(A\text{-}a)_{O_2}$ is increased, and Pa_{O_2} is reduced. In patients with moderate to severe left ventricular failure these values are normal. The increase in oxygen uptake/minute ($\dot{V}_{O_2}$) in relation to the increase in work rate ($\dot{V}_{O_2}$/WR) progressively slows in PPH patients below the normal rate of 10 ml/min/Watt, leading to a decreasing $\dot{V}_{O_2}$/WR. In moderate to severe left ventricular failure for instance $\dot{V}_{O_2}$/WR is initially already low.[62]

TREATMENT

Treatment of pulmonary hypertension should consist of treatment of any causative disease, as well as the hypertension itself. Generally, mild pulmonary hypertension, i.e. mean pressure less than 30 mmHg, is not treated with the current therapeutic agents.[59] Severe pulmonary hypertension should be treated to alleviate symptoms and possibly to extend survival. It is important to prevent circumstances that may aggravate pulmonary hypertension. Exercise should be limited and guided by symptoms. High altitude exposure and medication that worsens pulmonary hypertension must be avoided.[18,20,31] Air travel is considered safe in pressurised aeroplanes, although supplemental oxygen may be needed. Medication that interferes with anticoagulant therapy should not be used, not even medication that enhances the degree of anticoagulation, such as non-steroidal anti-inflammatory drugs.[20] The haemodynamic changes of pregnancy are badly tolerated and can worsen the disease. Therefore female patients must be advised to prevent pregnancy, and should use reliable contraceptive methods. The use of oral contraceptives must be discouraged, because of the increased risk of thrombosis and therefore aggravation of the disease. Supplemental oxygen is necessary when a patient is hypoxic at rest or during exercise, because hypoxic pulmonary vasoconstriction contributes to the pathogenesis of pulmonary disease. Anticoagulants are indicated because PPH patients are at risk of thrombotic events, due to impaired mobility and right heart failure.[31] Even survival may be improved by using anticoagulants.[55,63] The recommended international normalised ratio (INR) must be between 2.0 and 3.0.[31,59] Subcutaneous heparin may be an alternative when coumarins are contraindicated. Diuretics can be used to control peripheral oedema, caused by the increased vascular volume of advanced right heart failure, or secondary to high-dose calcium-channel blocking agents. However, care should be taken to maintain a sufficient right ventricle pre-load, as excessive diuresis can lead to a reduced cardiac output. Digoxin is sometimes used to counteract the negative inotropic effects of some of the calcium-channel blocking agents.[55] Rich *et al.* recently showed a favourable effect of digoxin, with an increase in cardiac output and a significant reduction in norepinephrine levels.[64]

As vasoconstriction plays an important part in the pathogenesis of PPH, much attention has been given to vasodilator therapy. Effect of vasodilator therapy in an individual patient is unpredictable; acute vasodilator testing is therefore important, also because the responses to acute challenge with vasodilators are predictive for the long-term response to oral vasodilator therapy.[20] The most suitable drugs for testing acute responses are short-acting, and titratable vasodilators, such as epoprostenol, nitric oxide, and adenosine.[16] Characteristics that predict a long-term response to oral calcium-channel blockers are reduction in pulmonary artery pressure with an unchanged or improved cardiac output and an unchanged systemic blood pressure in response to nitric oxide or epoprostenol.[20] Less than 30% of all patients respond to these vasodilators. Lack of response to epoprostenol, does not rule out a positive response to chronic vasodilator therapy, probably due to effects on vascular growth, remodelling, or platelet function, next to vasodilatation.[56,65]

Mostly calcium-channel blockers are used as oral vasodilators, because their principal action is on vascular smooth muscle.[59] Nifedipine and diltiazem are most commonly used, and are administered in high doses. The use of calcium-channel blockers is limited by their depressant effect on myocardial contractility and the chance of rebound pulmonary hypertension after abrupt discontinuation. Despite these drawbacks, calcium-channel blockers remain the oral drugs of choice in treating PPH.[59] Ninety-four percent of patients who responded to high-dose calcium-channel blockers were still alive after five years, as compared with 55% of the patients who did not respond.[55] Angiotensin-

converting enzyme inhibitors are not recommended because of disappointing results.[16,31,59] Nitric oxide is a potent pulmonary vasodilator with little systemic vasodilating activity, because it binds to haemoglobin in the pulmonary vascular bed. At the moment it is only available in a gaseous form, and therefore not a suitable option for long-term therapy. L-arginine, a precursor of nitric oxide which can be taken orally, might be a possible treatment option in the future.[66]

Prostacyclin and analogues are a promising therapy for patients with PPH. Prostacyclin is a potent natural vasodilator and platelet aggregation inhibitor produced by the endothelial cells. Barst *et al.* showed that long-term continuous intravenous prostacyclin therapy increased exercise endurance for a prolonged period of time. The six-minute walking test was on average improved by 100 meters after six months intravenous prostacyclin, and was maintained at 18 months. This improvement was correlated to reductions in right heart pressures. Three-year survival was 63% in the treatment group, compared with 41% in the historical control group.[65] Higenbottam *et al.* showed that continuous intravenous treatment of epoprostenol or iloprost, with or without calcium-channel blockers, prolonged survival compared with conventional treatment with anticoagulants.[67] Twelve weeks of continuous intravenous epoprostenol (prostacyclin) therapy in combination with conventional therapy (anticoagulants, oral vasodilators, diuretic agents, digoxin, and supplemental oxygen) versus conventional therapy alone, showed an improvement in exercise capacity (six-minute walking test increased 32 m versus a decrease of 15 m in the conventional group); pulmonary artery pressure and pulmonary vascular resistance were reduced by 8% and 21% respectively, with an increase of 3% and 9% respectively, in the conventional group; and an improved survival in the epoprostenol group.[56] McLaughlin *et al.* showed a reduction in pulmonary vascular resistance with long-term (more than one year) therapy with intravenous epoprostenol that exceeded the reduction caused by vasodilator challenge. Even in patients with no short-term response to acute vasodilator challenge, long-term epoprostenol reduced pulmonary vascular resistance, suggesting a possible reversal of the vascular lesions by epoprostenol.[68] Wax *et al.* showed an increase in exercise capacity at up to 27 months of continuous infusion of epoprostenol.[69] The use of continuous intravenous epoprostenol has, apart from its high costs, two major disadvantages. Over time the dose of epoprostenol needs to be increased to maintain its effects,[65,68] and continuous infusion of epoprostenol requires a central venous catheter with a portable pump. Potentially this may lead to complications, such as infections, catheter thrombosis, and pump failure. Recently, long-term treatment with aerolised iloprost, a stable prostacyclin analogue, has shown similar beneficial effects on exercise capacity and haemodynamics.[70] Haemodynamics and pulmonary gas exchange can be positively influenced by sildenafil, a phosphodiesterase type 5 inhibitor.[71] Wilkens *et al.* used a combination of inhaled iloprost and oral sildenafil, showing an improvement in haemodynamic parameters. They suggest that sildenafil may be used as an adjunct to prostaglandin treatment.[72] Channick *et al.* studied the effect of an orally active antagonist of endothelin receptor A and B (bosentan). Bosentan, twice daily, increased exercise capacity and improved cardiopulmonary haemodynamics.[46]

Surgical treatment of primary pulmonary hypertension consists of atrial septostomy and lung transplantation. Atrial septostomy is not yet a standardised treatment, and is performed by balloon or blade septostomy.[59] Recurrent syncope, despite maximal therapy, may be an indication. Clinical improvement, as well as increased cardiac index, is reported.[51] Although systemic arterial oxygen saturation decreases, oxygen delivery improves because of the increased cardiac output. Ultimately, patients may require lung transplantation. Single lung, double lung, and heart-lung transplantation have all been used in the treatment of PPH. (Heart-) lung transplantation has its limitations, such as the use of immunosuppressive medication with many side effects. One-year survival is 70% and three-year survival is 50-60% in transplanted patients with PPH.[59]

In conclusion, primary pulmonary hypertension is a rare vascular disease of unknown origin. Much research has been performed lately into the origins and therapy of this disease, but our therapeutic approaches are still limited.

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ORIGINAL ARTICLE

Hypogammaglobulinaemia: cumulative experience in 49 patients in a tertiary care institution

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ABSTRACT

In this paper, clinical data of 49 adult patients with agammaglobulinaemia (syn. hypogammaglobulinaemia), 15 cases of X-linked agammaglobulinaemia (XLA) and 34 of common variable immunodeficiency (CVID) are reviewed. Although immunoglobulin substitution largely abolished life-threatening respiratory tract infections, considerable infectious and non-infectious morbidity was still encountered in these patients. Almost all patients suffered from chronic or recurrent upper and lower airway infections, mainly caused by *Haemophilus influenzae* and pneumococci. The lower respiratory tract infections led to cumulative damage to the respiratory tract, especially in XLA patients. Also the incidence of infections outside the respiratory tract (giardiasis, *Campylobacter jejuni* infections) was more common in XLA patients than in CVID patients. Nodular lymphoid hyperplasia was only found in CVID. A variety of other non-infectious complications were seen especially in CVID.
Neoplastic complications occurred in nine patients (two cases of thymoma, two colorectal cancer, one gastric carcinoma, two haematological malignancies, two cases of skin cancer). Six patients died (five XLA patients and one CVID patient, from infectious and non-infectious causes).

INTRODUCTION

In 1952 Bruton described the first case of hypogammaglobulinaemia (syn. agammaglobulinaemia).[1] The mode of inheritance of this immune disorder appeared to be X-linked and the susceptibility to infection was apparent during the first years of life. Two years after Bruton's publication, Janeway *et al.*[2] reported a type of agammaglobulinaemia which did not seem to have a distinctive genetic pattern and affected both sexes equally; the first symptoms and signs of this form can appear at any age. In the current WHO classification, the latter form of agammaglobulinaemia is referred to as common variable immunodeficiency (CVID), whereas Bruton's sex-linked agammaglobulinaemia is called X-linked agammaglobulinaemia (XLA).[3]

We now know that XLA is caused by a mutation in the gene encoding for Bruton tyrosine kinase (syn., B-cell tyrosine kinase, BTK). Due to dysfunctional BTK, the differentiation from pre-B cells to B-cells is virtually absent.[4-6] The defect in CVID is probably heterogeneous. At least in a large proportion of cases a defect in the ability of T cells to stimulate B cells to produce antibody is assumed.[7,8] Different classifications of CVID have been proposed, but until more is understood of the pathogenesis, the validity of these is questionable. Despite these differences in pathogenesis, XLA and CVID both lead to humoral immunodeficiency, which makes affected individuals susceptible to infections.[9] In addition, in both conditions non-infectious morbidity is seen. Nowadays, patients with XLA and CVID have a good prognosis, provided they receive immunoglobulin substitution.[10,11] In this paper, we review the spectrum of clinical manifestations of hypogammaglobulinaemia that still occur despite immunoglobulin substitution and availability of antibiotics in a patient population composed of adolescents and adults cared for in a single tertiary care centre in the Netherlands. The differences and similarities in the clinical manifestations of XLA and CVID are discussed.

* J.W.M. van der Meer was not involved in the handling and review process of this paper.

PATIENTS AND METHODS

The Department of General Internal Medicine at the University Medical Centre Nijmegen serves as a supra-regional centre for primary immunodeficiencies, taking care of one of the largest populations of adolescent and adult patients with primary immunodeficiencies in the Netherlands. Records of patients with primary hypogammaglobulinaemia within the Department of Internal Medicine were reviewed. Patients with hyper IgM (Rosen type) agammaglobulinaemia were excluded from this study because this is a distinct disease entity with a very low prevalence. Patients with selective IgA deficiency were also excluded. The remaining patients (n=49) met the criteria for either XLA (n=15) or CVID (n=34). XLA was diagnosed according to the criteria of the WHO report:[3]
1. Male patients presenting with pyogenic infections in infancy or early childhood.
2. Levels of all isotypes of immunoglobulins are markedly decreased or absent.
3. The number of circulating B cells is low and plasma cells are absent and number and function of T cells are unaffected.
Patients with proven BTK mutation or with an affected male relative were also classified as having XLA. CVID was diagnosed as a form of primary hypogammaglobulinaemia in which XLA was excluded. It was taken into account that both sexes are equally affected in CVID and first symptoms can become clinically manifest at any age, although most cases of CVID occur in the second, third, and fourth decade; normal numbers of circulating B cells are usually found but plasma cells are usually absent and serum IgG concentration is strongly decreased, while IgA and IgM concentrations can be normal or decreased.
For this study, we reviewed the patient records and scored the clinical manifestations, and subdivided these in the following categories: infections and infectious complications, non-infectious inflammatory disorders, neoplasia and miscellaneous disorders. In addition, mortality was scored.

RESULTS

Characteristics of patients

The characteristics of the patients are shown in *table 1*. By definition all XLA patients were males. Of the 34 CVID patients, ten were male (29%) and 24 female (71%). Ten of the 15 XLA (67%) patients were diagnosed before the age of six while four patients with proven BTK mutations and symptoms since early childhood were not diagnosed until the age of 7, 12, 15 and 19. The age at time of diagnosis of CVID patients is normally distributed, between eight months and 63 years.

Table 1
Characteristics of 49 hypogammaglobulinaemic patients

		XLA	CVID
Gender	female	0	24
	male	15	10
Median age at present time		45.6	48.5
Median age of onset (yrs)		1.2	26.5
Median age of diagnosis (yrs)		6.5	34.3
Disease duration (yrs)		35.4	15.8

All patients received intravenous IgG substitution every three to four weeks. The substitution dose was set to maintain trough concentrations of IgG ≥5 g/l; if infections persisted the dose was increased (either by enhancing the dose or by shortening the dosage interval). Because of the retrospective nature of this case series, and the non-standardised substitution, data on IgG concentrations after substitution are not presented here.

Infectious complications

Both XLA and CVID patients experienced infections of the upper and lower respiratory tract and of the gastrointestinal tract. Sepsis and infections of the urogenital tract, central nervous system and skin tract were less common, but do occur (*table 2*).

Table 2
Infectious complications in 49 hypogammaglobulinaemic patients

	XLA (n=15)	CVID (n=34)	TOTAL (n=49)
Ear, nose, throat			
Sinusitis	10	22	32
Otitis media	8	15	23
Eyes			
Conjunctivitis	5	2	7
Lower respiratory tract			
Pneumonia	15	30	45
Gastrointestinal tract/abdomen			
Infectious diarrhoea	11	13	24
Giardiasis	7	9	16
Pneumococcal peritonitis	0	1	1
Urogenital tract			
Cystitis	3	9	12
Balanitis	1	0	1
Skin			
Pityriasis vesicolor	2	1	3
Erysipelas-like lesions	2	3	4
Herpes zoster	1	2	3
Impetigo	1	0	1
Arthritis	0	1	1
Meningitis	4	1	5
Sepsis	4	2	6

Respiratory tract

All XLA patients suffered from ear/nose/throat infections, while 23 of the CVID patients had ear/nose/throat infections. Especially sinusitis and otitis media were commonly encountered (*table 2*). Lower respiratory tract infections occurred in all XLA patients and in nearly all CVID patients (30). The causative organisms are listed in *table 3*. The most common organisms found were the encapsulated bacteria *Haemophilus influenzae* and *Streptococcus pneumoniae*. After institution of immunoglobulin substitution, life-threatening pulmonary infections were very rare. Following recurrent or chronic pulmonary infection, many patients developed destructive lung disease (*table 4* and *figure 1*). COPD occurred in three XLA patients and in eight CVID patients. Bronchiectases proven by bronchogram or HR CT scanning were found in twelve XLA patients and in eight CVID patients. The microflora of these patients did not differ from patients without bronchiectasis.

In patients with respiratory tract symptoms, pulmonary function tests were performed on a regular basis, the frequency of testing was determined by the severity of the pulmonary involvement.

Respiratory tract infections manifested by purulent sputum and/or fever and infiltrates on the chest X-ray were treated with antibiotics aiming at pneumococci and *H. influenzae*. The antibiograms of previous cultures were taken into account for the choice of the empirical antibiotic treatment. Occasionally patients, especially those with bronchiectasis, received maintenance therapy with antibiotics because of frequently recurring exacerbations of infection. In recent years, many patients were given prescriptions and instructions for self-initiated antimicrobial treatment, to be started at the first symptoms of exacerbation.

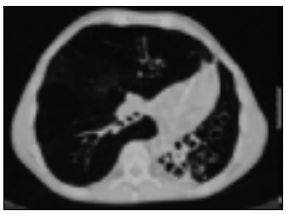

Figure 1

Destruction of the lungs in a 38-year-old patient with XLA

There is a marked shift of the mediastinum to the left. Bullous lesions, bronchiectases and an inhomogeneous perfusion can be seen.

Gastrointestinal tract

Eleven XLA patients and 13 CVID patients suffered from chronic or frequently recurring gastroenteritis (*table 2*). *Salmonella* spp. and *Campylobacter jejuni* were the most common causative organisms (*table 3*). *Giardia lamblia* occurred in the stools of seven of the XLA patients and nine of the CVID patients. Other infections encountered were oral candidiasis (two XLA and two CVID patients), candida oesophagitis (two CVID patients) and bacterial overgrowth (one CVID patient). Causative organisms of gastrointestinal infections are listed in *table 3*. Lymphonodular hyperplasia (LNH) was a common endoscopic or roentgenographic finding in CVID patients (n=6) that was not seen in XLA patients (*figure 2*).

Table 3

Micro-organisms identified causing infections in 49 hypogammaglobulinaemia patients

	XLA (n=15)	CVID (n=34)	TOTAL (n=49)
Respiratory tract			
Haemophilus influenzae	14	17	31
Streptococcus pneumoniae	8	9	17
Moraxella catarrhalis	0	4	4
Mycoplasma pneumoniae	1	1	2
Enterobacteriaceae	1	4	5
Pseudomonas aeruginosa	0	2	2
Staphylococcus aureus	0	1	1
β-haemolytic *streptococcus*	1	0	1
Gastrointestinal tract/abdomen			
Campylobacter jejuni	6	5	11
Salmonella spp.	1	4	5
Giardia lamblia	7	9	16
Clostridium dificile	0	1	1
Streptococcus pneumoniae	0	1	1
Candida spp.	3	3	6
Strongyloides stercoralis	0	1	1
Taenia saginata	0	1	1
Microsporidium	0	1	1
Enterovirus	0	1	1
Bloodstream			
Haemophilus influenzae	1	0	1
Streptococcus pneumoniae	0	2	2
Campylobacter jejuni	3	0	3
Multiple organisms	0	1	1
Candida guillemondi	0	1	1

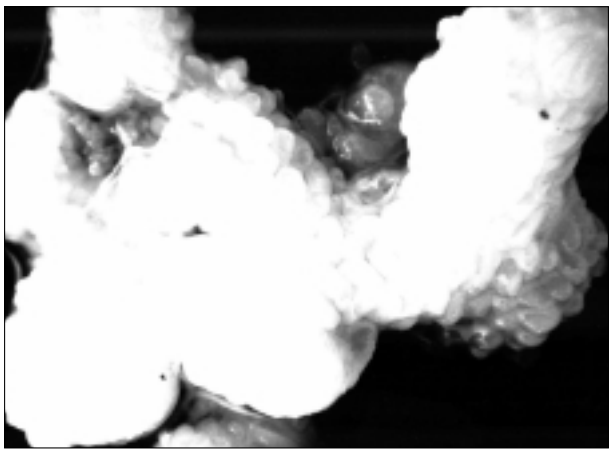

Figure 2
X-ray picture of lymphnodular hyperplasia of the small intestine as visualised by enteroclysis (courtesy of Professor J.B.M.J. Jansen, University Medical Centre, Nijmegen, the Netherlands)

Table 4
Pulmonary complications of recurrent infections in 49 hypogammaglobulinaemic patients

	XLA (n=15)	CVID (n=34)	TOTAL (n=49)
Bronchiectasis	12	8	20
COPD	3	8	11
Fibrosis	4	1	5

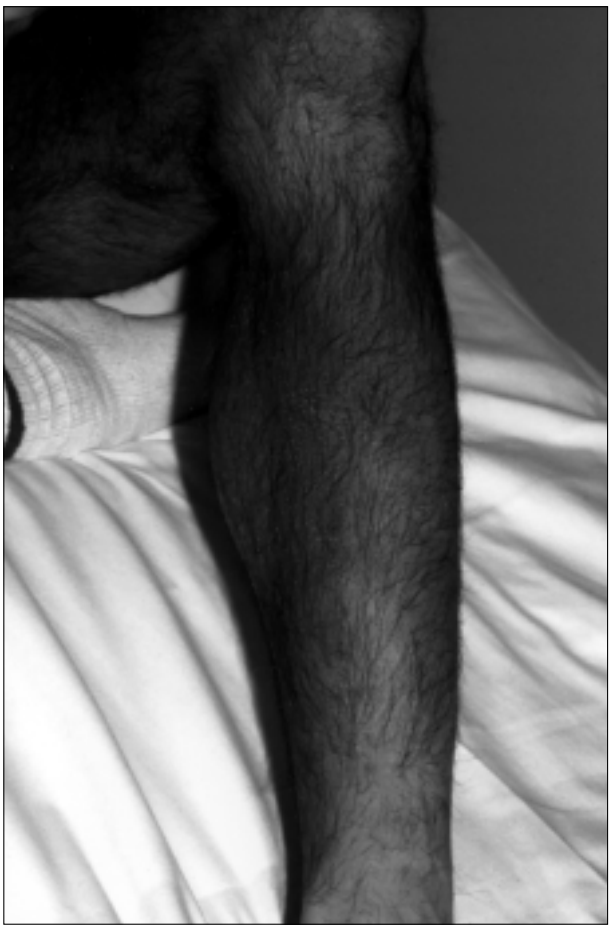

Figure 3
Erysipelas-like skin lesion in an XLA patient with Campylobacter bacteraemia

Urogenital tract
The most common urogenital infection was cystitis: three XLA and nine CVID patients suffered from at least one episode of cystitis. Two of the nine CVID patients were male. *Citrobacter freundii* and *Escherichia coli* were both cultured twice from the urine. One XLA patient had a severe *Ureaplasma urealyticum* infection that affected the bladder, the prostate, the epidydimis and the urethra. One other XLA patient had candidal balanitis. Candida vaginitis was found twice, adnexitis once. Other causative organisms were rare.

Skin infections
Skin infections are fairly common in agammaglobulinaemia. Four XLA and three CVID patients suffered from *Staphylococcus* skin infections. Pityriasis vesicolor was seen in two XLA patients and in one CVID patient. Two XLA patients and three CVID patients had erysipelas-like skin lesions due to *C. jejuni* (*figure 3*) and one XLA patient had impetigo. Uncomplicated zoster was seen in one XLA and in two CVID patients.

Sepsis and CNS infections
Meningitis was seen in six patients; in two XLA patients, it was caused by *S. pneumoniae*. No causative organism could be determined in two other XLA patients and two CVID patients. Four cases of septicaemia were encountered in the XLA group, three caused by *C. jejuni* and one by *H. influenzae*. One CVID patient suffered from pneumococcal sepsis and arthritis before substitution was installed. While on total parenteral nutrition because of severe unexplained diarrhoea and malabsorption, one CVID patient developed sepsis caused by multiple organisms, i.e. *Staphylococcus epidermidis, Fusobacterium oryzahabitans, Enterobacter cloacae, Klebsiella pneumoniae, Micrococcus varians* and *Candida guilliermondi*, the last mentioned being the cause of death. One CVID patient had *S. pneumoniae* sepsis.
One XLA patient developed progressive multifocal leucoencephalopathy while on glucocorticosteroids (Netea-Maier *et al.*, manuscript in preparation).

Other infections

Other infections encountered were infectious mononucleosis (two cases of CVID), a splenic abscess caused by *Yersinia enterocolitica* and *Bartonella henselae* infection in one XLA patient. Malaria occurred once (with an uneventful course) in a CVID patient. One CVID patient suffered from infective arthritis; the causative organism was *S. pneumoniae*. One XLA patient had a mild cirrhosis from chronic hepatitis B.

Non-infectious disorders

Neoplasia

In the XLA group two patients were diagnosed with colorectal carcinoma.[12] This finding was a reason to perform colonoscopies in all XLA patients. Two CVID patients had thymoma (*figure 4*). Non-Hodgkin's lymphoma, T-large granular lymphocyte leukaemia (in a patient who had been operated before for thymoma), spinocellular carcinoma of the skin and basal cell carcinoma were each found once in the CVID group (*table 5*).

Table 5

Non-infectious disorders in 49 hypogammaglobulinaemic patients

	XLA (n=15)	CVID (n=34)
Neoplasia		
Thymoma	0	2
Colorectal carcinoma	2	0
Gastric cancer	0	1
Non-Hodgkin's lymphoma	0	1
T-large granular lymphocyte leukaemia	0	1
Basal cell carcinoma	0	1
Spinocellular carcinoma	0	1
Non-infectious immune disorders		
Haemolytic anaemia	0	4
Pernicious anaemia	0	2
Pyoderma gangrenosum	2	0
Neutropenia	0	1
Thrombocytopenia	0	1
Diabetes mellitus type I	0	1
Graves' disease	0	1
Crohn's disease	0	1
Polymyalgia rheumatica	0	1
Sarcoid-like lesions	1	0
Splenic enlargement	0	7
Aortic aneurysm (thoracic)	0	1

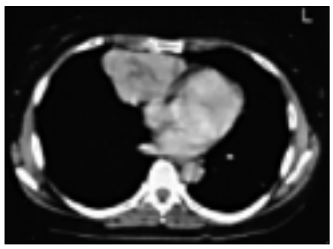

Figure 4

Thymoma in a patient with CVID (courtesy of Dr. E.F. Ullman and Dr. E.H. Ströbbe, Rijnstate Hospital, Arnhem, the Netherlands)

Because of the high risk of gastric cancer in CVID, gastroscopies were performed at least once in CVID patients. Dependent on the findings (atrophy/metaplasia), the interval for follow-up endoscopy was determined. Gastric carcinoma was diagnosed early in one CVID patient, who was *Helicobacter pylori* positive; so far she seems to have been operated radically.

Non-infectious immune disorders

CVID is often accompanied by non-infectious disorders, such as sarcoid-like granulomatous lesions, neutropenia, autoimmune anaemia and thrombocytopenia, splenic enlargement and hyperthyroidism. These phenomena were found in our CVID patients (*table 5*). In the XLA group, one patient was diagnosed as having sarcoid-like lesions. Two cases of pyoderma gangrenosum were seen in the XLA group (*figure 5*). In one patient splenic abscesses were found with positive immunofluorescence for *Yersinia enterocolitica*. Although the patient showed a response to high-dose immunoglobulin therapy and skin grafting, the pyoderma did not fully resolve until the patient underwent a partial splenectomy to remove the abscesses.

Causes of death

Five XLA patients and one CVID patient died (*table 6*). Two patients died from colorectal carcinoma.[12] One patient died from pneumonia at the age of 37 due to severe destructive lung disease, another XLA patient died in his sleep probably due to alcohol intoxication. One XLA patient died after a rapid progressive neurological disorder. Postmortem investigation revealed progressive multifocal leucoencephalopathy due to JC virus. One CVID patient died from candidal sepsis as a complication of parenteral nutrition.

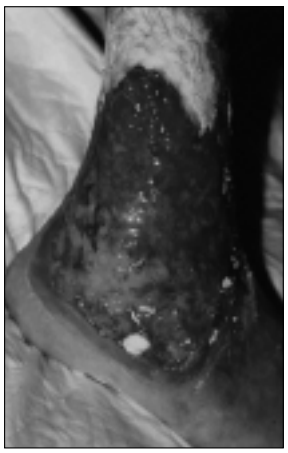

Figure 5
Pyoderma gangraenosum in a patient with XLA

Table 6
Causes of death in hypogammaglobulinaemic patients

GENDER	DIAGNOSIS	AGE	CAUSE
Female	CVID	29	Candida sepsis
Male	XLA	30	Colorectal carcinoma
Male	XLA	36	Colorectal carcinoma
Male	XLA	37	Alcohol intoxication
Male	XLA	37	Pneumonia with severe bronchiectasis
Male	XLA	49	Progressive multifocal leucoencephalopathy

DISCUSSION

From this study, which describes the cumulative experience with 49 patients with hypogammaglobulinaemia, it becomes clear that, despite the availability of intravenous IgG, there is still an impressive morbidity and mortality. Upper and lower respiratory infections, mainly caused by the encapsulated bacteria *Haemophilus influenzae* and *Streptococcus pneumoniae*, are the most commonly encountered manifestations of disease in both groups. These findings are in concordance with previous studies,[13-18] underlining the importance of humoral immunity in the defence against encapsulated bacteria. Recurrent infections cause cumulative damage to the lower respiratory tract and lead to destructive lung disease.[19] In our population this was observed more frequently in XLA patients than in CVID patients, probably as a consequence of the longer history and the more profound defect in the former group. This is, however, in contrast with one report by Sweinberg *et al.*, who found a higher incidence of chronic pulmonary disease in CVID patients than in XLA patients.[20] In CVID patients the occurrence of destructive lung disease correlated with disease duration.

The incidence of infections outside the respiratory tract also seems to be higher in XLA than in CVID. Apart from the longer mean disease duration, this could be caused by the more profound deficiency of immunoglobulins in XLA, both in the circulation and at the mucosal sites. In contrast with the literature, we found a relatively high incidence of giardiasis in the XLA group compared with the CVID group. In an investigation of 96 XLA patients, giardiasis was confirmed in only nine patients.[14] In another report, in which XLA and CVID patients were evaluated, giardiasis was found in 19 out of 240 CVID patients and in only one of 44 XLA patients.[15] An important factor in the defence against *Giardia lamblia* is IgA.[21,22] As mentioned above, IgA is absent in XLA, and therefore a high incidence could be expected. This is underscored by our observation that in the CVID group giardiasis was only found in patients whose IgA levels were undetectable (<0.05 g/l, n=15) or unknown (n=8). In patients with detectable numbers of IgA (>0.05 g/l, n=7) no giardiasis was found.

IgA also plays an important role in the defence of the gastrointestinal tract against *C. jejuni*.[23] *C. jejuni* was found more frequently in XLA (n=6) than in CVID (n=5). In the CVID group, *C. jejuni* was only found in patients with undetectable IgA (n=3) or unknown IgA levels (n=2). In hypogammaglobulinaemic patients carrying *C. jejuni* in their intestines, fever episodes may be seen that are due to *C. jejuni* bacteraemia. In this series, this was seen in four patients; reports on three of these patients were published earlier.[24,25] This infectious complication seems to be due to a lack of bactericidal activity in hypogammaglobulinaemic plasma; in normal plasma this bactericidal activity seems to reside in IgM that is able to bind to *C. jejuni* and activates complement.[24,26]

A well-known but unexplained endoscopic finding in CVID patients is nodular lymphoid hyperplasia (NLH).[27] In six patients NLH was demonstrated. Since not all patients underwent endoscopy this is probably underestimated. The aetiology of this phenomenon is unknown. An association with chronic giardiasis has been suggested,[28,29] but this could not be confirmed by others.[12,30] No association between giardiasis and NLH was present in our population, neither did we find an association with other pathogens. In the XLA group no NLH was found despite the fact that all patients except one underwent endoscopy.

An increased incidence of cancer is a well-known feature of agammaglobulinaemia.[31-33] One patient suffered non-Hodgkin's lymphoma. In a prospective study on the incidence of cancer in immunodeficiencies there was an approximately 30-fold increase of lymphoma.[33] T-large granular lymphocyte leukaemia[34] developed in one patient who previously suffered from thymoma. In the XLA group two patients had colorectal carcinoma. The

increased risk of colorectal carcinoma in XLA has been reported from our centre before;[12] these two patients were reported in that paper. The incidence of colorectal cancer for patients with XLA is estimated to be 30-fold greater than that of the normal population. Because of this increased risk colonoscopy was offered to all XLA patients and performed in all but one. No precancerous abnormalities of the colon were found. In biopsies obtained from these patients, however, low levels of colonic glutathione S-transferase, an enzyme that presumably protects against neoplastic transformation, were found.[35] From the prospective study of cancer in patients with hypogammaglobulinaemia, there was an estimated 47-fold increased incidence of gastric cancer.[36] One case of early gastric cancer in a patient with CVID was found in our population. Interestingly, this patient had a normal gastrin when injected with the peptide hormone bombesin. Thus, the so-called bombesin test does not distinguish between patients at risk and those not at risk for gastric cancer.[37]
Much has been written on the high incidence of non-infectious immune phenomena in CVID, often referred to as autoimmune diseases. We found some of these phenomena in our CVID population, although these diseases were relatively infrequent compared with other studies.[13,15-17] There is no satisfying explanation for this observation.
It is noteworthy that we found two XLA patients who suffered from *pyoderma gangrenosum*. As far as we know *pyoderma gangrenosum* has not been linked to XLA before. The pathogenesis is unclear. In one patient it may have been due to a concomitant splenic abscess caused by *Yersinia enterocolitica*. The pyoderma did not fully resolve until the patient underwent a partial splenectomy to remove the abscesses.
Overall CVID and XLA are disabling diseases that cause damage in the long run. Long-term treatment is effective in preventing life-threatening infection, but cannot prevent recurrent infection of the respiratory tract that can cause destructive lung disease. This problem seems to be more severe in XLA patients than in CVID patients and the importance of substitution with relatively high dosages of intravenous immunoglobulins has recently been stressed.[38]

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ABOUT THE COVER

Lithograph

GERDIEN KROES

This month's cover shows a lithograph by Gerdien Kroes. Gerdien (1963) works in Arnhem, the Netherlands, where she originally attended the Academy of Art. She exhibits her work at many individual and group exhibitions in the Netherlands (De Gele Rijder in Arnhem, Outline in Amsterdam, Verre Horizonten van Dichtbij in Zevenaar, Huize Erica in Bennekom) and abroad (Die Städtische Galerie Peschkenhaus in Moers/Germany, Exhibit of the Euregio Art Award 2000 nominations, Artoll in Bedburg-Hau/Germany). She has received several grants.

Her art does not try to tell a story, but rather depicts human and animal figures that belong in another, painted world. The figures have their own characters and seem to tell about their state of mind; the artist attempts to display the intensity of the figure's life.

The basis of her work is any kind of pictorial material, like movies showing the struggle for life, and photographs (taken by the artist herself). For her interpretation, Gerdien Kroes simplifies, distorts and changes the original image.

A limited edition of original prints of this month's cover is available at a price of € 200.

You can order the print at Galerie Unita, Rijksstraatweg 109, 6573CK Beek-Ubbergen, the Netherlands or by e-mail: galerie-unita@planet.nl.

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CASE REPORT

Cushing's syndrome caused by topical steroid therapy for psoriasis

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ABSTRACT

A 72-year-old woman developed manifestations of Cushing's syndrome after long-term topical steroid therapy for psoriasis. Shortly after tapering the dose of topical steroids she developed signs of adrenal insufficiency (provoked by a urinary tract infection) requiring intravenous administration of a stress dose of hydrocortisone. There have only been a few reports of systemic side effects of topically applied corticosteroids in adults. Considering their serious consequences physicians should be alert to signs of Cushing's syndrome in patients on long-term topical steroid therapy. Furthermore, clobetasol propionate ointment doses exceeding 50 g a week should not be prescribed and use of occlusive dressings should be avoided.

INTRODUCTION

Unexpected systemic glucocorticoid side effects caused by corticosteroids applied by enemas or via intra-articular injections have been reported in the literature.[1,2] Comparable effects arising from the use of topical corticosteroid therapy have been described a few times, mostly in children,[3-6] but also in adults.[7-15]

In this case report we present an adult patient who developed Cushing's syndrome with suppression of the hypothalamic-pituitary-adrenal (HPA) axis after long-term use of a topical synthetic glucocorticoid in the treatment of psoriasis.

CASE REPORT

A 72-year-old woman was referred to our hospital because of progressive oedema of both legs. Her medical history revealed extensive psoriasis since the age of 28. In the past, local therapy with coal tar products and with dithranol formulations, UVB phototherapy and UVA photochemotherapy (PUVA) were not successful. She had been previously treated with acitretin and methotrexate causing liver damage, fumaric acid leading to eosinophilia and cyclosporin for which she developed intolerance.

During the past three years clobetasol propionate 0.5 mg/g ointment had been applied daily on large parts of her trunk, arms and legs. Some months before admission she experienced a period of acute pain in the lower back, which resolved after two weeks.

During the few months before referral progressive oedema had developed in both legs. She denied chest pain, dyspnoea or orthopnoea. In addition she had noticed weakness of the legs and spontaneous bruising on her extremities. There had been an increase in weight over the last three years.

On admission her medication consisted of enalapril, furosemide, ibuprofen and clobetasol propionate ointment.

On physical examination clear signs of Cushing's syndrome were present with moon face, buffalo hump, kyphosis of the thoracic spine, central adiposity and extensive atrophy of both muscles and skin. Ecchymoses were present on the extremities and both legs showed pitting oedema until just below the knees.

Only a few psoriatic lesions were present on the legs and trunk.

Blood pressure was 180/95 mmHg, pulse 80, weight 98.6 kg, length 1.63 m and body mass index 37.6 kg/m^2.

Central venous pressure was not elevated and there were no signs of left-sided heart failure.
Laboratory results were as follows (normal values in parentheses): Hb 7.3 mmol/l (7.2-9.8), WBC 13.3x10^9/l (4.0-11.0), with predominance of neutrophils and lymphopenia in the differentiation, Na 139 mmol/l (136-146), K 4.0 mmol/l (3.5-4.5), glucose 3.9 mmol/l (3.5-6.0), creatinine 81 mcmol/l (<95), albumin 29 g/l (35-47), LDH 495 U/l (<475) and alkaline phosphatase 174 U/l (<105).
Liver enzymes and function were normal. A morning serum cortisol concentration was below 0.05 mcmol/l (0.14-0.55). Chest X-ray showed a normal sized heart and no signs of congestive heart failure. A CT scan of the abdomen was normal, without signs of inferior caval vein compression. X-rays of thoracic and lumbar spine showed multiple hyperlucent vertebrae suggestive of a decrease in mineral density. Furthermore the corpus of the twelfth thoracic vertebra was codfish shaped, probably caused by a recent compression fracture. The 25-hydroxy-vitamine D level was slightly decreased: 27 nmol/l (30-100). Dietary intake of calcium was estimated to be 1000 mg a day.
Treatment was initiated with calcium supplementation, vitamin D and alendronate. Diuretics were increased and the clobetasol propionate treatment was tapered over a period of two weeks by the consulting dermatologist.
Prednisone in a substitution dose of 5 mg a day was added to the medication at the same time in order to prevent clinical adrenal insufficiency. Shortly after release from the hospital she was readmitted with a urinary tract infection. She presented with signs suggestive of adrenal insufficiency, consisting of high fever, nausea and vomiting. Blood pressure was 115/65 mmHg, with a heart rate of 90 bpm. Plasma electrolyte concentrations were normal: Na 141 mmol/l, K 4.5 mmol/l. Haematology showed both eosinophilia (0.8x10^9/l, normal <0.4) and lymphocytosis (3.1x10^9/l, normal <3.0). All symptoms resolved rapidly after intravenous administration of a stress dose of hydrocortisone.
Now two years after the first admission, she is currently without topical glucocorticoid treatment and is substituted with 5 mg of prednisone a day. Her weight has decreased to 90 kg, blood pressure has normalised and the oedema disappeared spontaneously. Her psoriasis has become worse after tapering the clobetasol ointment and the skin is now treated with emollients and vitamin D analogues.

DISCUSSION

The history and clinical findings in our patient led us to the conclusion that she was suffering from Cushing's syndrome, caused by long-term high-dose topical administration of clobetasol propionate. Furthermore, the low cortisol level on first admission and the findings suggesting an Addisonian crisis on withdrawal of topical steroids in combination with a urinary tract infection showed that her hypothalamic-pituitary-adrenal axis must have been suppressed.
Oral glucocorticoid therapy is the most common cause of Cushing's syndrome.[16] Inhalation, rectal administration and intra-articular injection of glucocorticoids have also been reported to be sufficient to cause clinical hypercortisolism.[1,2,17] Although systemic side effects of topically applied corticosteroids are much more commonly noticed in children, this phenomenon has been described in adults several times.[7-15] There is some evidence that these systemic side effects are dose-dependent. When using low-dose clobetasol propionate in adults, usually few adverse systemic effects occur.[8] However, even when less than 50 g of clobetasol propionate ointment a week is applied, transient suppression of the hypothalamic-pituitary-adrenal axis may occur. Reduction of corticosteroid absorption when the epidermal barrier is restored has been suggested to be the reason why the effect is temporary in such cases.[8,18]
Patients needing over 50 g of clobetasol propionate ointment a week, usually because their psoriasic lesions cover a large part of their body surface area, are clearly at risk of developing Cushing's syndrome.[7,8]
Adrenal suppression, the second clinical problem of exogenous hypercortisolism, has also been found in patients using less potent topical corticosteroids especially when combined with the use of occlusive dressings, which enhances corticosteroid absorption.[19]
As adrenal suppression can lead to severe symptoms and even death, early diagnosis of Cushing's syndrome in patients using long-term topical steroids is very important.[20] Measurement of morning serum cortisol is the first diagnostic test. Dynamic testing, such as an insulin-tolerance or metyrapone test, must follow an equivocal result. Treatment of psoriasis depends on various individual circumstances, such as the type, extent, duration and natural history of the disease. Stable discoid psoriasis should first be approached with topical therapy. Tar preparations, vitamin D analogues, dithranol formulations, tazarotene ointment and a combination of these products can be used. More intensive tar or dithranol therapy (day-care unit) or UVB phototherapy are considered in more severe cases. If the above measures have failed, PUVA therapy or systemic medication with methotrexate, retinoids, cyclosporin or even corticosteroids are sometimes necessary.
Topically applied corticosteroids are of established value in psoriasis. In appropriate concentrations they are the treatment of choice on the scalp, face and neck, and genitalia.[21]
To prevent serious systemic side effects of topical steroid therapy it has been suggested that short intensive courses are given to induce rapid healing.[8] When applied for longer periods of time, clobetasol propionate ointment in doses of

no more than 50 g a week should be prescribed and use of occlusive dressings should be avoided.
When iatrogenic Cushing's syndrome is suspected from the history or physical examination, laboratory confirmation is mandatory in the light of the serious consequences missing this diagnosis can have, in particular when chronic topical steroid therapy is (abruptly) stopped without continuing clinical and laboratory control.

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CASE REPORT

Four cases of a secondary Cushingoid state following local triamcinolone acetonide (Kenacort®) injection

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ABSTRACT

Intra-articular, paratendinous or other soft tissue corticosteroid injections are well-recognised treatment modalities for rheumatic conditions in which a debilitating inflammatory component persists. A corticosteroid injection that is locally administered only sporadically evokes adverse effects. We report four cases of secondary Cushingoid state, twice due to single, and twice due to repetitive triamcinolone acetonide (TCA: Kenacort®) injection. A consulted general practitioner, internist and gynaecologist were not aware of the possibility that such a local injection may evoke a Cushingoid state with moon face, buffalo hump and/or disturbance of the menstrual cycle. Therefore we describe here the four cases we recently encountered.

INTRODUCTION

Local injections of corticosteroids are often used in the treatment of various inflammatory locomotor disorders. A notable part of injected corticosteroid, however, may be absorbed systemically.[1-3] This absorption may cause systemic effects, i.e. a secondary hypercortisolism or Cushingoid state with moon face, buffalo hump, gain of weight, as well as a disturbance of the menstrual cycle. Iatrogenic hypercortisolism has been reported secondary to accidental overdose of a depot corticosteroid,[4] but also secondary to therapeutic dosage of a depot injection intradermally,[5-7] intramuscularly, [8-11] as well as following intra-articular corticosteroid depot application,[12] particularly after repetitive injections.[13] Recently, even psychosis has been described following intra-articular injection of corticosteroid.[14]
Dutch pharmacy departments encountered a temporal delivery problem of depot preparation triamcinolone hexacetonide (TCH: Lederspan®) in 1998. During that period the TCH injectate was replaced by triamcinolone acetonide (TCA: Kenacort®). Following the application of TCA, four cases of secondary hypercortisolism were observed within a short period of time between 1998 and 1999; similar cases were not seen in the period prior to and after the TCH delivery problems of 1998, during which time TCH was most frequently used. Recently, in the summer of 2001, delivery problems with TCH were announced again. Production and delivery of triamcinolone acetonide (TCA: Kenacort®) was and still is normal.
Several physicians are not aware of the aforementioned side effects, as in literature this kind of sequelae is not always mentioned.[15]
The patients we will describe consulted general practitioners as well as general internists and gynaecologists, who were not aware that a local TCA depot injection is capable of evoking a clear Cushingoid state. We therefore describe four cases here and give a short review of the literature.

CASE PRESENTATIONS

Case 1

A 48-year-old female was seen in the outpatient department because of pain in the right and later left shoulder. On

physical examination she had a painful arc without signs of capsulitis. Abduction stress tests were positive in provoking this pain. Ultrasonography revealed a mild supraspinate tendinitis. Local injection of 40 mg TCA (Kenacort®) dissolved in 4 ml of lignocaine 2% resolved the pain of the right shoulder within three days. Five weeks later she asked for a similar injection in the left shoulder because of identical left-sided pain. Again 40 mg TCA (Kenacort®) in 4 ml of lignocaine 2% was administered. About ten days later she gradually developed a moon face, flushing at the coeur, palpitations with dyspnoea, tremors and disturbed menstruation. She gained about 8 kg in weight. On consultation about two months later the moon face with buffalo hump and flushing were still present. Laboratory tests: $ACTH_{8\ a.m.}$ <1.1 pM (normal value 1-55 pM), cortisol levels showed flattening: 30 nM at 8 a.m., and 20 nM at 4 p.m. (normal values: 150-700 nM and 100-400 nM respectively). On consultation about six months later, all symptoms and signs had regressed, including the moon face and buffalo hump.

Case 2

A 42-year-old female was seen in the outpatient department because of chronic pain in the shoulders during elevation. On physical examination she had multiple tender points in accordance with the ACR criteria of fibromyalgia. She also had a painful arc without signs of capsulitis. Impingement syndrome was seen with a painful abduction stress test. Ultrasonography revealed mild cuff degeneration with mild supraspinate tendinitis. A local, paratendinous injection of 40 mg TCA (Kenacort®) dissolved in 4 ml of lignocaine 2% was given. About two weeks later she gradually developed a moon face. She gained about 5 kg in weight. In about three months symptoms and signs gradually regressed.

Case 3

A 28-year-old female was seen in the outpatient department because of pain located at the right buttock. On physical examination she had a pyriformis syndrome; sacroiliac stress tests were normal. Local injection with 40 mg TCA (Kenacort®) in 5 ml lignocaine 2% was given. In the two weeks thereafter she developed a moon face with buffalo hump and acne-like eruptions. Her weight increased by approximately 6 kg. For a period of two months her (previously normal) menstrual cycle was disturbed.

Case 4

A 19-year-old female was seen in the outpatient department because of a debilitating pain in buttocks. On physical examination she had a bilateral pyriformis syndrome; sacroiliac stress tests were normal. A right-sided local injection with 40 mg TCA (Kenacort®) in 4 ml lignocaine 2% was given. About five weeks later she asked for a similar injection into the left pyriformis region. In the two weeks thereafter she developed a moon face, buffalo hump, and acne-like eruptions. She gained about 6 kg. For a period of three months her menstrual cycle was disturbed. Signs and symptoms gradually diminished in the following six months.

DISCUSSION

Local injection of corticosteroids is frequently used in clinical rheumatology in an ultimate attempt to reduce pain due to local inflammatory responses of arthritis, bursitis, or tendinitis. A significant dose of locally injected corticosteroid may, however, be absorbed systemically. The systemically absorbed dose may evoke a secondary hypercortisolism similar to Cushing's syndrome. Patients who developed a Cushingoid state about two weeks later often indicated that they did not associate this with the injection. Reviews even state that a 'Cushingoid state ... is not seen in patients receiving three or four joint injections per year'.[15] Not only rheumatologists, but also general practitioners, gynaecologists and internists should realise that this association really does exist prior to performing an extensive work-up in these patients.

In our experience, side effects occur more frequently following the 40 mg TCA (Kenacort®), than following 20 mg TCH (Lederspan®) injection. Equipotency studies in dermatology aim at vasomotor effects, but well-performed anti-inflammatory equipotency data of these drugs are still lacking in literature. For data on the duration of the anti-inflammatory effect of some currently available corticosteroid preparations following intra-articular application, see *table 1*.[16,18]

Table 1

Currently available corticosteroid preparations and duration of anti-inflammatory effect after intra-articular administration[16]

PREPARATION	1 ML	MEAN DURATION OF EFFECT
Betamethasone acetate	6 mg	9 days
Dexamethasone acetate	8 mg	8 days
Methylprednisolone acetate	40 mg	8 days
Prednisolone tebutate	20 mg	14 days
Triamcinolone acetonide	40 mg	14 days
Triamcinolone diacetate	25 mg	7 days
Triamcinolone hexacetonide	20 mg	21 days

Only depot preparations with effects exceeding seven days are tabulated.

Early signs supporting significant systemic absorption of locally administered corticosteroids include a clinical improvement of distant joints in a polyarthritis, a transient eosinopenia, and increased levels of urinary metabolites. Koehler *et al.* described hypothalamic-pituitary-adrenal axis suppression following the intra-articular administration of 4 mg of dexamethasone or 4 mg of methylprednisolone acetate.[2] Others have demonstrated that suppression of endogenous cortisol production in children may last from 10 up to 30 days.[17] Higher serum levels of the injectate have been found in patients in whom the dose was divided into two joints rather than administering it into a single joint;[1] a putative potentiation effect of divided doses has been attributed to a greater absorptive surface area in the divided-doses regimen. Further well-known adverse effects are a postinjection flare, cutaneous atrophy at the site of injection, local calcifications, hypersensitivity reactions, local bacterial infection, avascular necrosis and tendon rupture following injection in or near a tendon.
We recommend all clinicians to be aware of potential Cushingoid side effects following local corticosteroid injection, and that patients are asked about recent injections when referred for analysis of a Cushingoid state. Furthermore we recommend our colleague rheumatologists and orthopaedic surgeons to use corticosteroid depot injections with caution.

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Uncertainty in medicine: Phoenix Hippocrates

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DECISION-MAKING IN THE FACE OF UNCERTAINTY

Doctors have always had difficulties in applying their experience and knowledge to patient care. When hunting-gatherings gave way to agriculture, and epidemics raged,[1] they must have consulted their close colleagues, the priests: what particular evil spirit was at large, punishing their people? And in antiquity, puzzled and worried by an unusual illness, they must have wondered: which of the four humours? Hippocrates summed up this ever-present difficulty in medical practice – never knowing enough for 'everycase' – ars longa, vita brevis (first aphorism, first line). Translated, it could be put as follows: you will never see and treat enough cases to avoid every error in your practice. Hippocrates collected case histories, so acquiring clinical experience. (Analogous to English case law, providing precedents.) He tried hard to educate his pupils, and introduced bedside teaching, advising emphatically: 'Make frequent visits...' and 'When you examine the patient, inquire into all the particulars...'[2]

If Hippocrates could have met William Harvey, he would have been excited about the blood circulating through the body, forced by the heart. Talking to the Reverend Bayes, he would have been interested in likelihood ratios, though mystified by the Arabic numerals. Yet he would not have changed his curriculum on Cos, with bedside teaching as its centre. Certainly, he would have been impressed, if other time travels were possible, by cells and the messages exchanged between them. He would have understood that laws of chance make uncertainty explicit. Time for one more excursion? Then to the nearest Cochrane Centre! He would have been convinced that knowledge about the mechanisms of disease could lead to ideas about new treatments; and that the evidence from clinical trials about their effectiveness[3] increased the power of medicine enormously: 'evidence-based medicine'. But he would have maintained that this future would not change the last line of his first aphorism: decision difficult. He knew that bedside teaching would remain the best available method for teaching diagnosis, prognosis and treatment. If Hippocrates had read Immanuel Kant (extracted from a shorter text), he would have known that his problems were due to the difficulties of selecting the correct 'category' from experience, knowledge and evidence, to apply in this particular case. Why are you so sure that in this case too much phlegm is the problem. Again, how do you know that in this case your diet works? Is it not different from previous patients with the same complaints? The mental operation required for this is the opposite of generalisation; it is called 'individuation'. Used less than generalisation ('all patients feel ill'), individuation ('this person feels feverish') means individualising. This difficult mental operation, requiring experience and judgement, is best taught at the bedside.

PHOENIX, A MYTHICAL BIRD

Phoenix lived to the south-east of Greece, in a blessed place, serving the Sun God. Every thousand years it sang, at dawn. So beautiful was its song that the Sun God stopped. Starting again, his wagon sent sparks into the

nest of the Phoenix, who burnt to death. But from the ashes it rose again. Metaphors need to be used with caution, but Hippocrates can be seen as a Phoenix, reborn time and again. Sydenham (1624-1689), acclaimed as the 'English Hippocrates', prized observation at the bedside. Boerhaave (1668-1738), in the Netherlands likened to Hippocrates, pleaded for a return to bedside teaching, and made it Leiden's great attraction. Sir William Osler (1849-1919), deserving to be called the Canadian-American-English Hippocrates, once more reinstated the bedside as the centre of doctors' training. His dictum 'It is much more important to know what sort of patient has the disease than to know what sort of disease the patient has' still adorns medical lecture halls.[2] The clinicopathological conference is aimed at diagnosis; its learned acrobats have to find out what disease this particular patient has or had. In daily practice, more pedestrian and with less preparation, the doctor does the same in the clinical encounter, step by step. At night, browsing in his medical weekly, he likes to read the case reports.

WHEN IS AN ANECDOTE

When is an anecdote (not an anecdote?) was a paper in The Lancet, protesting against the low status of the case report.[4] Its last example was Phineas Gage, a capable and efficient foreman, who suffered an accident in 1848: an iron four-foot bar was blown through the front part of his head. He was carried to the doctor's surgery in an ox-cart, and walked from the cart to the doctor's office.

Amazingly, the damage to the frontal lobes had caused no motor or intellectual defect. However, Gage became fitful and vacillating, making plans for the future, which he soon abandoned for others. His former friends, for whom he now showed little consideration, concluded that he was 'no longer Gage'. This case, reported in the Boston Medical and Surgical Journal, led to the formation of the 'category' of patients with frontal lobe damage. Later still, this category led to reflection on the categories 'body' and 'mind'. At the time of publication it seemed an anecdote, its author suffering from anecdotage.[4]

THE CASE SERIES: OBSERVATIONAL, NOT CONTROLLED

The case series can add even more to our 'decision-base' than the single case. Diseases are 'the vehicles of our experience'[5] and the job of describing them, and their variations will never be finished. They have improved our expertise. Some examples, mainly from neurology and neurosurgery, will make this clear:

- 'subdural haematoma may present as TIA'
- 'neck stiffness may be lacking in 10% of meningitis patients'
- 'tremor may be absent in Parkinson's disease'
- 'multiple sclerosis may have a benign course'
- 'depression may look like dementia'
- 'lumbar puncture may cause subdural haematoma'
- 'patients with stroke may benefit from thrombolysis'
- 'patients in a vegetative state may wake up, even after a year'
- 'some antiepileptic drugs may cause agranulocytosis'

Even causes, and effective treatments, can be discovered by case series: herniation of the nucleus pulposus as the commonest cause of a common syndrome, sciatica; surgery as its effective treatment.[6] Both 'spectrum' and 'pattern' of diseases determine our decisions.[5] Both are continually refined, or changed, by cases or case series. New diseases, or sub-diseases, can be found by systematic observation of patients. Perimesencephalic haemorrhage was so discovered, albeit as a 'side effect' of a clinical trial.

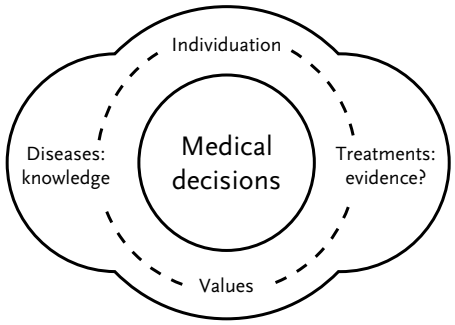
A benign sub-category of non-aneurysmal subarachnoid haemorrhage (SAH), with characteristic radiological features, it has a clinical course not complicated by rebleeding or infarction, and a good prognosis.[7] New treatments have also been discovered by case observations, before they could be tested by clinical trials, for example: i.v. immunoglobulin for some neuropathies.[8] 'Interesting' cases can lead to randomised controlled trials.[9] Changes in epidemiology can bedevil diagnostics: syphilitic dementia, once common and a simple diagnosis, moreover reversible if treated early, is now a diagnostic puzzle, suitable for clinicopathological exercise.[10] Description of 'Cases of apoplexy and lethargy with observations upon the comatose diseases', published by Cheyne in 1812, later extended, but then combined with pathophysiological principles, resulted in a modern classic on diagnosis, emergency management and prognosis of coma.[11]

Therefore, diseases could be called the 'units of medical research' (knowledge and evidence), and cases the 'units of medical practice' as well as the 'units of medical education', the best 'material' to learn individuation as defined above. Cases, especially patient demonstrations, teach the principles and practice of diagnosis and treatment, as Hippocrates knew. Cases and patient demonstrations detect diagnostic and therapeutic pitfalls: they function as error-prevention for individual cases, complementary to the system approach, which is more appropriate for preventing hospital disasters. Equally important, cases can generate questions for clinical research, and so contribute to the decision-base of the future. This division between cases and diseases is not black and white.

TOMORROW'S DOCTORS AND THEIR PATIENTS

Tomorrow's doctors will have to assimilate some fruits of the Human Genome Project. Now they already have to grasp the principles of genetic screening.[12] Then the Proteome will follow, and so on: doctors will have to keep in step. Equally important, they will have to keep applying the rules of clinical epidemiology and 'critical appraisal'. Evidence-based medicine, perceived by some as gospel, and in fact a great step forward,[3] will be practised more and more, after its catchword has gone out of fashion. Doctors can already turn to textbooks which are not only evidence-based, but also emphasise individuation in diagnosis and treatment.[13] They are learning to track down the best evidence for this case by computer, at the bedside, so to speak. These achievements will bring their concurrent dilemmas: in very premature babies with a risk of cognitive impairment; in very old people with chronic diseases often combined with dementia; in patients needing palliative treatment; and in the so-called worried well. Indeed, for those dilemmas, too, the centre of clinical training will remain at the bedside, its aim to acquire experience as an aid in clinical decisions. In recent decades, clinical judgement has once again been recognised as a crucial tool for doctors.[14]

Their patients will witness medical progress. They will also learn of healthcare rationing, the paradoxical price of scientific progress; it will require decisions involving assessment of relative value.[15] Already, statins, taxols, TNF blockers, AIDS medications and interferon beta present baffling choices. Patients will consult doctors who may be preoccupied with these choices and how to present them to society; perhaps with less interest for the patient as a person. However, in this age of personal autonomy, the patient will demand more attention for his/her preferences, sometimes choosing not to follow the doctor's orders. This change of attitude in patients will add to the complexity of decisions; thus strengthening Hippocrates' decision difficult. Growth of knowledge, more critical use of evidence, doctors trained in individuation, and the respect for patients' values will all contribute to the decisions made. Doctors will have to combine those four elements into a personal synthesis (*figure 1*). Research findings will have to be implemented more than they are now.[16]



- **Knowledge of the human body and its diseases: organs and cells, and mechanisms of diseases and their possible treatments, both medical and surgical.**
- **Knowledge on mechanisms of treatment is as important as 'evidence-based data'.**
- **Individuation: the opposite of generalisation; see text.**
- **The values of patients and doctors, made explicit (often 'shared decision-making').**
- **The stippled lines refer to the doctor's synthesis of these elements into decisions.**

Figure 1
Medical decisions are based on four elements (A medix was a local magistrate in Etruscan times, who sat in judgement on local difficulties and problems, and made decisions in the best interests of the parties concerned)

TOMORROW'S MEDICINE

The patient as a person, mentioned already, may demand a comeback. For him or her, the 'story' of an illness may have a personal meaning. Examples can be found in great novels: see for an example the *Appendix*. So-called narrative-based medicine will help to bridge the gap between this human side of medicine and the evidence-based kind;[17] see Osler's dictum. By strengthening this dimension, uncertainty will not diminish. Doctors will become advisers rather than prescribers, patients their own advocates rather than accepting any treatment. Uncertainty will thus be more explicit, once again. The more we know, the clearer it will be that we must choose: the evidence-choice paradox. Ethical issues are not confined to topics of public controversy, such as euthanasia, but met on every ward round.[18]

With values recognised as inherent to medicine, another vexing phenomenon, medical practice variation,[19] can then be tackled. Moreover, there are perspectives of better treatment, based on science;[20] meanwhile, our present medical practice may seem dehumanising to patients and their relatives.[20]

HIPPOCRATES AND THE FUTURE OF MEDICINE

In this brief sketch, I have emphasised the complexity of clinical decisions, requiring analysis as well as synthesis. If we consulted Hippocrates specifically on treatment, how would he react? Perhaps as follows: 'Ah, treatment, it always seemed to me more hazardous than diagnosis.[2] This afternoon I was surfing on Intertime, learning about your numerous new treatments, mostly advertisements. I also came across a book by a psychiatrist, specialised in

madness. He pointed out that "autistic" thinking of schizophrenics, based on fantasies rather than facts, is also present, more than dormant, in some doctors. They try so hard to treat that they cause harm.[21] Many of these will be eager to apply molecular biology today instead of tomorrow. Not my subject, but I am sure that Aristotle – a colleague's son, do you know him? – would love it. He would be working in biology and genetics – nice Greek words – and would believe in his latest experiments. He is interested in almost everything but medicine.[2] I will stick to systematic observation of my patients. I admit that your knowledge of infection contains some epidemics. However, Intertime has also taught me about epidemiology, concerning illness in people as a group. Male British doctors were followed for many years, and from those observations I have no doubt that it is good advice for men to stop smoking. They will avoid lung cancer. Perhaps for women too. Moreover, the study from a town across the ocean, Framingham, has convinced me that the same advice, combined with lifestyle and dietary measures, will help contain your epidemic of heart disease. Then "blood pressure" seems important, but I did not understand the term "risk factor": something like a Roman law code? Prevention of traffic accidents already seems to work (belts, helmets, and no wine). Your surgeons steadily improve their skills: hips, eyes, hearts, brain. Even cutting out cancers sometimes succeeds. I have always been cautious, but in my opinion you should be optimistic, with all your new laboratory techniques and all the work in progress. It may become feasible to prevent cancers, strokes and dementia. I myself have always thought that a good physician should cultivate the art of prognosis.[2] You seem to even study that scientifically, with definitions of "good" and "poor" outcomes, and "confidence intervals", measuring the remaining uncertainty.[22] All these developments will depend on clinical researchers.[23] Aristotelians and epidemiologists working together in mutual respect, focused on the problems, not on fame or finance. Meanwhile, your people will have to spend much more on medical research and healthcare, especially nursing and other (what you call) para-medical professions. By the way, I am not a mythical bird.'

THE TAMING OF UNCERTAINTY?

Neo-Hippocratic doctors may feel that decisions are as difficult as ever. That is the old idea of 'the art of medicine'. Uncertainty in decision-making can now be quantified, but not reduced. 'Decision analysis', a time-consuming method, can do this. Probabilities and 'utilities' are estimated, and their products calculated; the effects of assumptions are explored with so-called 'sensitivity analysis'.[24,25] This is an interesting method, but its results depend on such factors as the wealth of the country, the organisation of the health service, and on cultural norms.[26] Indeed, decisions will, I think, become more complex but at the same time more explicit; especially the decisions involved in developing clinical guidelines.[27] Today, under 'decision', PubMed offered 62,333 items. (Looking at the first groups of 20, it was striking that the word 'decision' was lacking in most titles.) In former times anatomy, physiology, biochemistry, pathology and pharmacology were dominant. Later, randomised controlled trials showed an exponential growth. Nowadays, genetics is the topic. However, clinical decision-making is also a growing subject. One of the first books on it appeared only 25 years ago.[5] If we exclude the Aphorisms.

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APPENDIX

'Confessions of Zeno', by Italo Svevo, is about the hero Zeno's struggle with his cigarette habit. Zeno argues with his psychoanalyst. Recalling every 'last cigarette' he has ever smoked, he describes his life as a failure. In real life the author Svevo (pen name of Ettore Schmitz) was killed in a road accident. In vain he asked for a smoke. 'That really would have been a last cigarette,' he said. And died.

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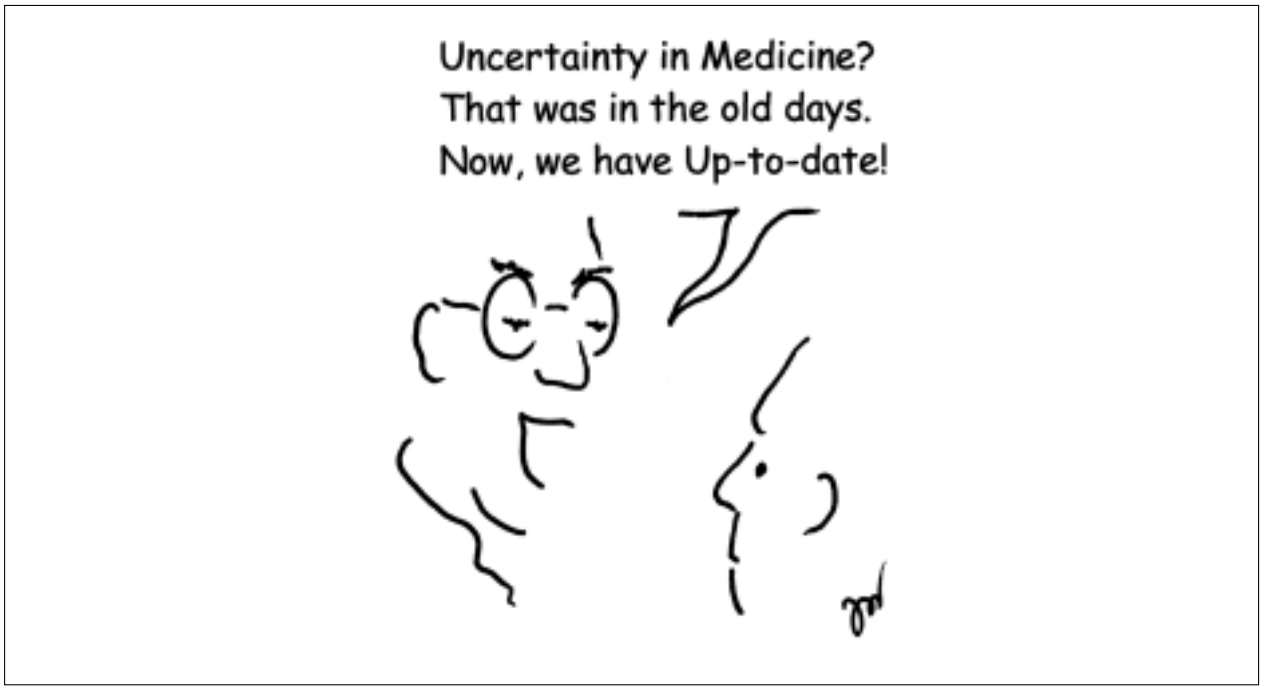

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The Netherlands Journal of Medicine publishes papers in all relevant fields of internal medicine. In addition to reports of original clinical and experimental studies, reviews on topics of interest or importance, case reports, book reviews and letters to the Editor are welcomed.

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The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

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Type all pages with double spacing and wide margins on one side of the paper. To facilitate the reviewing process number the pages; also we would appreciate seeing the line numbers in the margin (Word: page set-up - margins - layout - line numbers). Divide the manuscript into the following sections: Title page, Abstract, Introduction, Materials and methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

A *Covering letter* should accompany the manuscript, identifying the person (with the address, telephone and telex numbers, and e-mail address) responsible for negotiations concerning the manuscript: the letter should make it clear that the final manuscript has been seen and approved by all authors. Conflicts of interest, any commercial affiliations, consultations, stock or equity interests should be specified. In the letter 1-3 sentences should be dedicated to what this study adds. All authors should sign the letter.

The *Title page* should include authors' names, degrees, academic addresses, address for correspondence including telephone, fax and e-mail, and grant support. Also the contribution of each author should be specified.
The title should be informative and not exceed 90 characters, including spaces. Avoid use of extraneous words such as 'study', 'investigation' as well as priority claims (new, novel, first). Give a running title of less than 50 characters. If data from the manuscript have been presented at a meeting, list the name, date and location of the meeting and reference and previously published abstracts in the bibliography. Give a word count (including references, excluding tables and legends) at the bottom of this page.

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The *Abstract,* not exceeding 200 words, should be written in a structured manner and with particular care, since this will be the only part of the article studied by some readers. In original articles, the abstract should consist of four paragraphs, labelled Background, Methods, Results, and Conclusions. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

The *Introduction* should be brief and set out the purposes for which the study has been performed.

The *Materials and methods* should be sufficiently detailed so that readers and reviewers can understand precisely what has been done without studying the references directly. The description may be abbreviated when well-accepted techniques are used.

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Examples:

[1.] Smilde TJ, Wissen S van, Wollersheim H, Kastelein JJP, Stalenhoef AFH. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. Neth J Med 2001;59:184-95.

[2.] Kaplan NM. Clinical Hypertension. 7th Edition. Baltimore: Williams & Wilkins; 1998.

[3.] Powell LW, Isselbacher KJ. Hemochromatosis. In: Harrison's Principles of Internal Medicine, 15th Edition, Braunwald E, Fauci AS, Kasper DL, et al. (eds). New York: McGraw-Hill; 2001. p. 2257-61.

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