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Cover picture

THEOPHRASTUS, FATHER OF BOTANY (350 B.C.)

The Greek teacher and botanist, Theophrastus, systematized knowledge of herbs and plants, describing their medical qualities, preparations, and use. His students learned of nature by observing her treasures at firsthand.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

George A. Bender, Director Robert A. Thom, Artist

Drug allergy

Adverse reactions to drugs are common, affecting an estimated 2 - 30% of hospitalized patients. These reactions may be immunologic or non-immunologic. The latter include side-effects, intolerance, drug toxicity and idiosyncratic reactions. It is important to distinguish drug allergy from non-immunologic reactions. When a diagnosis of drug allergy is made, the most important aspect of management is avoidance of drugs with similar chemical structure.

Immunological basis for drug hypersensitivity

Immunologically mediated drug reactions result from the specific interaction of a drug or one of its metabolites with circulating IgG or IgM, IgE bound to mast cells or basophils or sensitized lymphocytes. The ensuing allergic reactions represent the clinical manifestations of inflammatory response (Table 1).

Table 1. Clinical manifestations of allergic reactions

Skin: Itching, urticaria, angio-oedema, vasculitis
Respiratory: Stridor, bronchospasm
Circulatory: Anaphylactic shock

Immunogenicity of a drug is related to both genetic factors and physical characteristics of the antigen (drug) itself. High molecular weight drugs are immunogenic without modification but most drugs are low molecular weight compounds (Table 2) that are not immunogenic unless modified through a process called haptenation, when a drug or its metabolite forms chemical bonds with the patient's cell surface, soluble proteins, and other molecules with free amino or sulfhydryl groups. The resulting complex or the haptenated drug is then recognized as foreign by the immune system and capable of an inducing an immunologic response.

Risk factors for allergy may be drug-related or patient-related. The route of administration and the pattern of exposure influence the sensitization, which is more with topical preparations due to high proficiency of antigen-presenting cells (Langerhans cells) in the skin. Surprisingly, atopic status does not increase the risk of immediate hypersensitivity to drugs, but a familial propensity to develop drug allergy has been reported.

Table 2. Some high and low molecular weight drugs

Low	*High*
Insulin	Penicillin
Heparin	Cephalasporin
Heterogenous or animal proteins	Sulphonaminde
	Phenytoin
	NSAIDs
	Metronidazole
	Thiouracil

The cardinal clinical features of atomy are eczema, rhinitis and asthma.

Genetic factors determining drug metabolism and certain human leukocyte antigen (HLA) phenotypes have been linked to increased allergy. Genetic or acquired differences in N-acetylation rate affect the risk of reaction to sulfonamides, hydralazine and procainamide. Concurrent disease or concomitant drug administration also affects the risk of reaction. Ebstein-Barr virus and human immunodeficiency virus (HIV) infection significantly increase the risk of cutaneous reactions respectively to ampicillin and sulfonamides. Despite the lack of CD4 lymphocyte in acquired immunodeficiency syndrome there is evidence that CD8 cytotoxic cells can produce the cytokines that enhance IgE-production, eosinophilia, or cell-mediated drug induced immunopathology. The range of frequent drug induced reactions in HIV infection includes fever, rash, anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and haematologic and hepatic reactions.

Immunologic classification

The clinical manifestations and their temporal relationship to drug exposure are important clinical clues in diagnosis. The Gell and Coombs classification of clinical hypersensitivity is especially useful for allergic drug reactions (Table 3).

Table 3. Gell and Coombs 1963 classification of immunopathology

Class	*Specific immune reactant*	*Mediators*	*Diseases*
I	IgE	Mast cells and basophil-derived	Atopy Urticaria/angioedema Anaphylaxis
II	IgG, IgM	Complement	Immune haemolytic anaemia, neutropenia, thrombocytopenia
III	IgG, IgM	Complement	Serum sickness
IV	T lymphocytes	T cell cytokines	Allergic contact dermatitis

Type I hypersensitivity

In a previously sensitized person, symptoms develop within minutes after drug exposure due to the release of mast cells and basophil-derived mediators (Table 4). If IgE antibodies are synthesized de novo during the course of drug treatment, the onset of clinical symptoms is delayed by days to weeks. About 90% of systemic type I allergic reactions include cutaneous features, such as generalized flushing, pruritus, urticaria, or antioedema.

Type II cytotoxic reactions

A circulating or bone marrow cell is affected as "innocent bystander" because the drug or drug-immune complex adhere to it, so that immune activation of complement results in lysis through the action of the "membrane attack complex" (C5-9). Methydopa induced, Coombs positive haemolytic anaemia is a classical example.

Type III hypersensitivity reaction

Circulating immune-complex deposition results in pathological process throughout the body (serum sickness), in tissues such as elastic lamina of arteries, glomeruli, articular cartilage and skin basement membrane. Products resulting from complement activation are strongly chaemotactic for polymorphonuclear leukocytes, which activate and produce reactive oxygen metabolites and proteolytic lysosomal enzymes. These inflammatory mediators cause vascular and tissue damage, which can be magnified if the clotting system is activated. The clinical manifestations (Table 5) typically appear 10 - 21 days after administration of the offending medication. The time course of the disease development reflects the generation of specific antibody, formation of immune-complexes, and a relative state of soluble antigen excess. The appearance of symptoms can be more rapid, in a matter of 2 - 4 days, when antibody is pre-existing because of previous sensitization.

Table 4. Mast cell and basophil derived mediators and their effects

Mediator	Clinical effect
Histamine	Vasodilatation, leak of fluid, bronchoconstriction
Leukotrienes	Bronchoconstriction
Interleukine - 5	Chaemotactic to eosinophils
Interleukine - 4	Immunoglobulin class-switching to IgE

Table 5. Clinical manifestations of serum sickness

Fever
Arthralgia
Lymphadenopathy
Glomerulonephritis
Vasculitis

In the days before the introduction of antibiotics, foreign animal serum was used as a treatment for infection, and about 50% of treated patients developed clinical serum sickness. At present, serum sickness is seen after administration of antivenom and low-molecular weight drugs (Table 2). The current use of foreign monoclonal antibody therapy for a wide variety of disorders has brought a resurgence of immune complex-mediated illness.

Type IV hypersensitivity reaction

Allergic contact dermatitis is a classic example. In cutaneous reactions, antigen (hapten-protein conjugate) is processed by antigen-presenting (Langerhans) cells, which interact with antigen specific T lymphocytes, stimulating the release of cytokines (IL-1, IL2 and INF-γ). These cytokines orchestrate the dermal inflammation resulting in acute as well as chronic skin reactions. The typical interval between exposure and clinical symptoms is 12 - 48 hours in sensitized patients, but the actual process of sensitization may take days to years depending on the intensity of exposure and the nature of the antigen (Table 6). An additive such as ethylene diamine or fragrance, rather than the drug itself, is commonly the allergen. Ironically, topical corticosteroids used to treat acute contact dermatitis, are occasionally contact allergens as well. Clinical features of acute Type IV hypersensitivity in the skin are erythema, pruritus, papules and vesicles. Excoriation, scaling and lichenification are chronic skin manifestations.

Drug induced photosensitivity can be either phototoxic (direct thermal injury) or photoallergic. Phototoxic reactions are not immunologic. Instead, a drug or its metabolite is transformed in vivo into a toxic compound by sunlight exposure, producing tissue injury that clinically resembles sunburn. In photoallergic reactions, solar radiation alters the drug (Table 6) or its metabolites in vivo forming a reactive compound or complete hapten that elicits an immune response. The rash is a Type IV eczematous lesion like allergic contact dermatitis. Some immunologic drug reactions do not easily fit the Gell and Coombs classification.

Drug fever can be caused through a variety of immunologic and non-immunologic mechanisms. Jarisch-Herxheimer reactions are febrile responses to pyrogens or endotoxins released by dying organisms. Fever may be caused by bacteraemia or a Jarisch-Herxheimer reaction in patients receiving antibiotics, but fever accompanied by eosinophilia and a rash with rapid defervescence after discontinuation of the drug suggests an immunogenic aetiology.

Table 6. Drugs causing allergic contact dermatitis and photoallergy

Allergic contact dermatitis	*Photoallergy*
Neomycin	Sulfonamides
Anaesthetic agents	Sulphonylurea
Para-aminobenzoic acid compounds	Chlorpromazine
Penicillins, sulfonamides	Frusemide
Bacitracin and chloramphenicol	Isoniazid
Transdermal medications: nitroglycerine and oestradiol	Naproxen
	Amiodarone

Acute interstitial nephritis (AIN) has been reported during therapy with methicillin and many other antibiotics that are not intrinsically nephrotoxic. NSAIDs, captopril, allopurinol, sulfonamides, rifampicin and phenytoin have also been implicated in AIN, which may present 10 - 20 days after initiation of therapy, and lead to acute renal failure, that may also be more occult and insidious in onset.

Autoimmune diseases can be initiated by a drug. Drug-induced lupus has been associated with procainamide, hydralazine, isoniazid, methyldopa and quinidine therapy. The majority of patients taking procainamide develop antinuclear antibodies, but fortunately only a small proportion actually develops clinical symptoms.

Diagnosis

The ability to confirm immunologic drug hypersensitivity is important in the diagnosis of a current suspected reaction and in the selection of a drug for future treatment (Table 7).

Table 7. Diagnostic procedure in drug allergy

1. Obtain history of reaction, including
   a. Time course
   b. Temporal relation to suspected drug(s)
2. List all current medication by
   a. Known propensity for allergy
   b. History of prior reaction in the patient
3. Classify the reaction as most likely
   a. Immunologic
   b. Pharmacologic
   c. Toxic
   d. Drug-drug interaction
   e. Idiosyncratic or intolerance
4. If most likely immunologic, classify by suspected immunopathologic mechanisms
5. Perform testing appropriate to the suspected mechanism
   a. Skin prick test or in vitro test, if available
   b. Patch testing for allergic contact dermatitis
   c. Test-dose challenge

Treatment

Acute rapid drug desensitization may be indicated in patients with a confirmed drug allergy, for which no satisfactory alternative treatment is possible (eg. aspirin desensitization before stenting for coronary artery disease). We have so far carried out 25 rapid aspirin desensitizations at the intensive care unit of Dr Neville Fernando Teaching Hospital with 100% success and only 2 patients developing mild reactions. Desensitization is achieved by administering progressive doubling doses of the drug at regular intervals (eg. every 15 minutes) until a therapeutic dose is tolerated. Oral administration carries a lower risk of life-threatening reactions. Premedication with antihistamine or steroids may mask early signs of anaphylaxis and allow dosing to proceed further than advisable.

Prognosis

The outcome of most cutaneous drug allergies is good after immediate cessation of the drug and symptom relief.

Drug induced anaphylaxis is potentially fatal, as it is characterized often by rapid onset (within minutes) cardiovascular collapse, especially in older patients. Other risk factors include cardiac pathologies associated with beta-blocker therapy. The true prevalence of fatal drug induced anaphylaxis is unknown, as the patients studied varied from children to adults, and from emergency room to ward inpatients, and most studies included all causes of anaphylaxis rather than specifically drug induced anaphylaxis.

Drug allergy may result in anxiety and impairment in health related quality of life for sufferers. Healthcare professionals involved in the care of patients with a history of drug allergy/hypersensitivity must be aware of potential long term psychological sequelae and effects on the doctor-patient relationships especially when new drugs have to be prescribed again.

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Managing osteoarthritis

Summary

Management of osteoarthritis should be based on a combination of non-drug and drug treatments targeted towards prevention, modifying risk and disease progression.

Obesity is the most important modifiable risk factor, so losing weight in addition to land- and water-based exercise and strength training is important.

While paracetamol can be tried, guidelines recommend non-steroidal anti-inflammatory drugs as first-line treatment for osteoarthritis. If there are concerns about the adverse effects of oral treatment, particularly in older patients or those with comorbidities, topical non-steroidal anti-inflammatory drugs can be used.

Glucosamine does not appear to be any better than placebo for pain. Its effect on the structural progression of disease when taken alone or in combination with chondroitin is uncertain. Fish oil has not been found to reduce the structural progression of knee arthritis.

Surgical interventions should be avoided in the first instance, with arthroscopic procedures not showing benefit over sham procedures or optimised physical and medical therapy. Joint replacement surgery should be considered for severe osteoarthritis.

Key words: capsaicin, chondroitin, glucosamine, non-steroidal anti-inflammatory drugs, opioids, osteoarthritis, paracetamol

*(Aust Prescr 2015; **38**: 115-9)*

Introduction

Osteoarthritis is a heterogeneous disease characterised by failure of the synovial joint including loss of articular cartilage, osteophyte formation, meniscal damage, ligamentous laxity and subchondral bone changes.[1] It is a chronic condition resulting from the interaction of multiple factors including genetic, metabolic, biochemical and biomechanical. Obesity is the single most important risk factor for knee osteoarthritis over other factors such as joint injury or genetic predisposition.

The management of osteoarthritis has shifted from the traditional approach of pain control to include interventions to improve tolerance for functional activity and quality of life. Optimal management involves non-drug and drug approaches that focus on preventing disease and stopping progression, as opposed to just targeting palliation of disease.[2]

Non-pharmacological management

After managing the pain, core interventions for all patients with osteoarthritis, with or without comorbidities, are land-based exercise, weight management, strength training, water-based exercise, self-management and education.[3] Exercise is universally recommended by clinical guidelines, and should be individualised after patient assessment. Meta-analyses have shown exercise to have small to moderate effect sizes for improved function and pain relief, similar to those achieved with non-steroidal anti-inflammatory drugs (NSAIDs) and analgesia.[4] Targeted muscle strengthening and general aerobic exercises are recommended, with water-based exercises suggested for those with functional and mobility limitations.[1,5] Stretching and flexibility exercises generally form part of an overall exercise program for osteoarthritis, to maintain or increase the range of motion in the joints. Supervised group or individual exercise is superior to independent home exercise for pain reduction.[6]

Mobility aids such as a stick (used in the opposite hand), knee braces and foot orthoses can also diminish pain and improve function.[7-9] Obesity is the single most important modifiable risk factor.[2,10] A meta-analysis found that a 5% decrease in weight within a 20-week period is beneficial for knee osteoarthritis.[11] A more recent trial showed up to a 50% improvement in symptoms with 10% weight reduction through diet and exercise.[12]

NSAIDs

NSAIDs are often considered to be the preferred first-line drug treatment for osteoarthritis. They have shown efficacy similar and superior to paracetamol.[13,14] Systematic reviews have found that NSAIDs are superior for rest pain and overall pain.[15]

The potential adverse effects of routine NSAID use are well documented. Gastrointestinal toxicity causes over 16 500 deaths and hospital admissions per year

in the USA.[16] Associated cardiovascular[17] and renal risks are also a concern. These risks pertain to both non-selective and cyclo-oxygenase (COX-2)-selective NSAIDs, even though COX-2 inhibitors have a better safety profile. A meta-analysis of 26 studies comparing the two found that COX-2 inhibitors reduced the relative risk of dyspepsia by 12% and the absolute risk by 3.7%.[18] Other systematic reviews confirm similar findings.[19]

The concomitant use of proton pump inhibitors with NSAIDs is generally recommended in patients with associated comorbidity risks. The same meta-analysis found that combining an NSAID with a proton pump inhibitor reduced the relative risk of dyspepsia by 66% and the absolute risk by 9% compared with an NSAID alone.[18]

The optimum duration of NSAID therapy is unclear. A meta-analysis of randomised trials[19] found no clear association between the duration of therapy with selective or non-selective NSAIDs and the risk of cardiovascular events. One small trial found continuous celecoxib use to be slightly more effective than intermittent use on pain and function, with similar rates of withdrawals due to adverse events.[20] No trials have been designed to assess serious gastrointestinal or cardiovascular harms associated with intermittent dosing strategies.

Paracetamol

Because of the adverse effect profile of NSAIDs, paracetamol (up to 4 g/day) has been the general analgesic of choice for mild to moderate pain in osteoarthritis for many practitioners. However, it is no longer recommended as first line by osteoarthritis guidelines.[3,21] A meta-analysis found low-level effects of paracetamol for pain management in osteoarthritis,[3,22] and a randomised controlled trial found paracetamol 4 g/day was no better than placebo for knee osteoarthritis.[23] In addition, increased safety concerns with paracetamol are arising, especially for patients with comorbidities. A 2012 review found an increased risk of gastrointestinal events and multi-organ failure with supratherapeutic doses, which are often taken for chronic pain.[24] Also, an analysis from the large prospective Nurses' Health Study found heavy use of paracetamol (>22 days/month) is associated with an increased risk of cardiovascular events (RR* 1.4, 95% CI† 1.1–1.6) similar to that with heavy use of NSAIDs (RR 1.4, 95% CI 1.3–1.6).[25]

Furthermore, there are concerns regarding gastrointestinal blood loss with concomitant use of NSAIDs and paracetamol. One study found the risk of gastrointestinal-related hospitalization was higher with combination treatment (HR‡ 2.55, 95% CI 1.98–3.28) compared with paracetamol alone (>3 g/day) (HR 1.20, 95% CI 1.03–1.40) and NSAIDs alone (HR 1.63, 95% CI 1.44–1.85).[26]

(* RR – Relative Risk; †CI – Confidence Interval; ‡ HR – Hazard ratio)

Topical therapies

The benefits of both topical NSAIDs and capsaicin are achieved through regular use, with recommended application of 3-4 times/day. There are associated local adverse effects including rash, burning and itching.

NSAIDs

Topical NSAIDs are appropriate for both knee and hand osteoarthritis as local drug delivery reduces gastrointestinal adverse reactions.[27,28] Efficacy is greater than placebo and comparable to oral NSAIDs.[28] Multiple formulations have been trialled including topical ketoprofen[29] and diclofenac sodium 1.5% topical solution in dimethyl sulfoxide.[27]

Safety with diclofenac sodium 1% gel has also been shown in the older population in a 12-month, post hoc analysis of patients with knee osteoarthritis. The overall rates of cardiovascular and gastrointestinal adverse events were similar for people under and over 65 years of age.[30]

To date, most studies have focused on individuals with knee-only osteoarthritis so the benefits of topical NSAIDs on people with multiple-joint osteoarthritis remain uncertain. Despite this, topical NSAIDs are increasingly being considered as a first-line pharmacological option, especially in patients with an increased risk of adverse events.

Capsaicin

Topical capsaicin can be used as an alternative or as an adjunct to standard drug treatment. Reviews of randomised controlled trials found that topical capsaicin is superior to placebo for knee osteoarthritis and reduces pain by 50%.[19,31] In general, a concentration of 0.025% capsaicin was better tolerated than 0.075%. Withdrawal because of an adverse event

was more common with capsaicin than with placebo (13% vs 3%).[31]

Intra-articular injections

Intra-articular corticosteroid injections provide shortterm pain relief (1-2 weeks in randomised controlled trials) and improved function for patients with osteoarthritis. They can be considered in patients who present with acute exacerbations with joint effusions and local inflammation. However, intra-articular injections given more frequently than once every four months can result in cartilage and joint damage,[32,33] as well as increased risk of infection.

The benefit of intra-articular hyaluronic acid injections is uncertain with inconsistent findings seen in metaanalyses. Trials showing benefit found varying effect sizes. A recent sensitivity analysis assessing blinded trials found only a small beneficial effect on pain.[34] The efficacy of corticosteroids is more significant than intra-articular hyaluronic acid in the short term. However in another comparison, hyaluronic acid provided longer-lasting benefit, extending beyond eight weeks.[35]

Opioids

Opioids are an alternative for patients who cannot tolerate or be prescribed first-line drugs because of contraindications due to comorbidities. Overall, systematic reviews concluded that oral and transdermal opioids were more effective compared to placebo in relieving pain and improving function in patients with hip and knee osteoarthritis. Benefits were small to moderate and adverse events caused many patients to withdraw. The usefulness of opioids in the long term is limited.[36]

Opioids have an increased risk of adverse events when compared with NSAIDs, including fractures (HR 4.47, 95% CI 3.12-6.41), cardiovascular events (HR 1.77, 95% CI 1.39-2.24) and all-cause mortality (HR 1.87, 95% CI 1.39-2.53).[37] When compared with placebo, patients were four times more likely to discontinue opioids due to an adverse event (RR 4.05, 95% CI 3.06-5.38).[36]

Duloxetine

The pain experienced in osteoarthritis is multifactorial. Often coexistent depression and neuropathic pain compound the overall pain syndrome. There is increased interest in centrally acting drugs such as selective noradrenaline and serotonin reuptake inhibitors. In a comparative trial, more people taking duloxetine reported reduced pain (by at least 30%) than those taking placebo (65% vs 44%).[38] Duloxetine can be a potential adjunct to conventional osteoarthritis treatment as additional pain reduction and improvement in function is seen when it is added to oral NSAIDs compared to placebo. Common adverse effects of duloxetine include nausea, constipation, fatigue, dry mouth and decreased appetite.[39]

Surgery

Joint replacement surgery should be considered for severe clinical disease with inadequate response to conservative treatment. Arthroscopic procedures for knee osteoarthritis have not provided additional benefit in people receiving physical and medical therapy.[40,41]

Complementary medicines

The most commonly used alternative treatment for osteoarthritis is glucosamine. In randomized controlled trials, it has a similar effect to placebo for pain, with independent trials showing smaller effects than commercially funded trials.[4] The Glucosamine/Chondroitin Arthritis Intervention Trial, a US National Institutes of Health-funded study, found that glucosamine was not significantly better than placebo in reducing knee pain (by 20%).[42] Evidence remains controversial regarding a possible structure-modifying effect (slowing or halting the progression of cartilage loss and other structural changes in the joint).

Similarly with chondroitin, its effect on symptomatic relief is uncertain – some reviews find an effect while others show no significant benefit over placebo.[43,44] Its ability to modify disease is also variable. Some studies found a reduction in the rate of decline in joint space width (0.07 mm/year, 95% CI 0.03–0.10).[45] Another trial found a statistically significant reduction in joint space narrowing after two years for a glucosamine/chondroitin combination compared to placebo. However, no statistical difference was found with individual treatment alone.[46]

Fish oil use is gaining popularity for osteoarthritis. While there are some trials in rheumatoid arthritis, its use in osteoarthritis remains uncertain. The components eicosapentaenoic acid (EPA) and docosa-

hexaenoic acid (DHA) reduced expression of degradative enzymes and inflammatory cytokines in in vitro cartilage models of osteoarthritis.[47,48] However, in a clinical study fish oil did not retard structural progression of symptomatic knee osteoarthritis at low or high doses.[49]

Newer therapies for osteoarthritis

There are numerous drug treatments for osteoarthritis, however their efficacy and adverse effect profiles often limit their use. At present there is no proven structure-modifying therapy available. The focus in osteoarthritis research is now shifting towards targeted biological therapies used in rheumatoid arthritis. As chronic forms of osteoarthritis are considered to be 'low' inflammatory conditions, research is underway into biological therapies targeting angiogenic factors, cytokines and pro-inflammatory mediators.

Different drugs targeting bone remodelling, including bisphosphonates and strontium ranelate, are also under investigation. Strontium ranelate reduced pain and radiological progression in randomised controlled trials.[50,51] However, in light of emerging data on cardiovascular risks, the potential benefits may not be justifiable.[52]

Commercial stem cell therapies have recently emerged for knee osteoarthritis. To date, there is no supportive evidence to advocate these treatments. Both the International Society for Stem Cell Research and Australian Rheumatology Association are against their current use for osteoarthritis.

Developing novel therapies for osteoarthritis is not without its challenges. Newer analgesics such as tanezumab, a nerve growth factor inhibitor, showed promise for improving pain and function in hip and knee osteoarthritis. However, the trials were halted after a small number of patients developed rapid joint destruction.[53]

Conclusion

There is a need for better therapeutic interventions for osteoarthritis. In the meantime, the management of osteoarthritis should be multifaceted, including nondrug interventions aiming at preventing disease and slowing its progression. If required, choosing optimal analgesia for an individual requires careful consideration and discussion regarding the relevant trade-offs.

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Evaluation of a child with short stature

Perceived shortness of a child is a common parental concern. Short stature becomes evident when a child starts attending a nursery or school. Evaluation of a child when there is concern about the stature is important, as appropriate treatment has to be instituted without delay to obtain maximum benefit.

To ascertain whether the child brought for assessment is really short, the first contact doctor should base the initial assessment on accepted definitions. As there is a genetic influence on stature, the child's height is interpreted in relation to the parents' height and the height of siblings.

Anthropometry and documentation

The standing height in children over 2 years of age is measured using a wall-mounted stadiometer according to published instructions [1]. The weight is also recorded initially and during follow up. The measurements of the child and siblings should be recorded on an appropriate growth chart [2]. To demonstrate a possible genetic influence on the stature, the target height (TH) and TH range are calculated based on the parents' height [3].

Eg: Target height for girls → (Mother's height +father's height -13cm) ÷ 2

Target height for boys → (Mother's height father's height + 13cm) ÷ 2

Target height range = TH ± 8.5cm

Whom to investigate?

A detailed history will exclude a chronic illness involving the renal, cardiac or respiratory systems. A detailed examination will reveal conditions such as syndromes associated with short stature (Turner syndrome, Down syndrome), inborn errors of metabolism such as mucopolysacharidoses and disorders involving the skeleton such as achondroplasia and chondrodysplastic syndromes. Undiagnosed untreated congenital hypothyroidism can also be detected by examining the child, and assay of TSH and f T4.

A short and obese child needs to be investigated for a possible endocrine disorder such as Cushing syndrome and disorders affecting the parathyroid gland. Even if the cause is obvious, evaluation is indicated to confirm the diagnosis and advise parents. When the condition is not obvious from the history and examination, serial anthropometric measurements on a growth chart are essential for initial evaluation and follow up.

Growth chart as a tool for evaluation

Short stature is defined as the height being more than 2 standard deviations below the population mean or below the 3rd percentile for age and sex [4]. Serial measurements of the height have to be plotted on the growth chart. Further investigations are indicated if the following are present –

- Very short with height < -3 SD
- Serial measurements show progressive deviation from the normal
- Height velocity <4cm/year
- Tall parents – consider the TH/THR

Panel 1. Causes of short stature

- Genetic or familial short stature
- Growth delay or constitutional delay in growth ± puberty
- Malnutrition/Intrauterine growth retardation (IUGR)
- Long-standing systemic illness
- Chromosomal disorders
- Syndromes
- Disorders of bone development
- Iatrogenic
- Psychosocial deprivation

Endocrine causes

- Hypothyroidism
- Growth hormone deficiency
- Cushing syndrome
- Untreated congenital adrenal hyperplasia, precocious puberty (initially tall as children, if untreated short adults)

The following should be documented (Panels 2 and 3).

Panel 2. History and examination

History

- Consanguinity/affected siblings/still births/ unexplained deaths
- Development
- Onset of puberty – parents/child
- Drugs

Examination

- Accurate height and weight measurements
- Height velocity – cm/year
- Dysmorphic features
- General examination and examination of the systems
- Funduscopy/visual field assessment
- Pubertal staging
- Heights of parents

Panel 3. Important measurements

Important measurements

- Length/height – serial measurements
- Weight
- Height velocity
- Upper segment/lower segment
- Skin fold thickness
- Height of parents

Height velocity (approximate)

- Mean 5 to 6 cm/year
- Puberty 10 to 12 cm/year

Body proportions

- Birth 1.7:1
- 2 years 1.44:1
- 4 years 1.25:1
- 8 years 1:1

Panel 4. Investigations

- Hb%/blood picture
- Serum creatinine/serum electrolytes/urine analysis
- CXR/ECG/Echocardiogram
- Skull x-ray – lateral (calcification of a craniopharyngioma)
- Skeletal age – at initial evaluation and during treatment/follow up
- Karyotype – any girl with short stature irrespective of the presence/absence of the Turner phenotype
- When indicated – TSH/fT_4, growth hormone (GH) provocative tests (a single assay of GH is of no value)

Management

Management would depend on the identified cause. Principles of management would be

- Treat if possible
- Discuss treatment and possible side-effects with parents and child
- Follow up with serial measurements (ideally by the same observer)
- Continue treatment – adjust dose/assess side-effects of the medication/assess effect of therapy/ evaluate for new physical signs
- Reassure parents/child throughout treatment

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Self-assessment questions

(Reference values are in parentheses)

Question 1

A 53-year old woman with a history of irritable bowel syndrome and gastro-esophageal reflux disease, has had episodes of breathlessness during the past two weeks. She was brought breathless at rest to the ETU by her relatives. Her respiratory rate was 35 per minute, and the blood pressure 150/70 mmHg. Auscultation of the heart and lungs revealed no abnormalities. The PEFR and chest xray were normal. Her arterial blood gases breathing air were as follows:

pH	7.58 (7.35 – 7.45)	HCO3 16.0 mmol/l (22 – 30)
PaO_2	13.0 kPa (10 – 13)	Base excess – 3.8
$PaCO_2$	3.0 kPa (4.5 – 6)	O2 saturation 98.2%

What is your diagnosis?

Question 2

A 74-year old man with a 2 -year history of thirst, polyuria, and nocturia, had the following laboratory test reports with him when he consulted a general physician.

Hb	10.7 g/dl
Corrected calcium	2.20 mmol/l (2.20 – 2.65)
PO_4	2.40 mmol/l (0.8 – 1.4)
Alk phosphatase	268 IU/l (40 – 140)

What are your initial thoughts on the data?

Question 3

A 63-year old woman with a history of hypertension and diabetes for 5 years presented with weakness of her left arm and leg for about 24 hours. She did not lose consciousness, and her speech was normal. She was on losartan, gliclazide, atorvastatin and aspirin. On examination she had hemiparesis of the left arm and leg, and a right-sided lower motor neurone facial palsy. A brain CT-scan showed only lacunar infarcts in both basal ganglia.

(A) Is the CT-scan of brain indicative of the site of the lesion?

(B) What imaging investigation may localise the site of the lesion?

Answers to self-assessment questions

Question 1 The blood gases are consistent with acute respiratory alkalosis. This woman is unlikely to have a cardiac or respiratory cause for her episodic hyperpnoea.

Question 2 Taken with the medical history, hyperphosphataemia, hypocalcaemia and anaemia should signal chronic kidney disease (CKD). The raised alkaline phosphatase is compatible with osteomalacia, a feature of bone disease in CKD.

Question 3 This medical history suggests acute cerebral infarction, and the clinical features are those of a "crossed hemiplegia" caused by a lesion in the pons. The Millard-Gubler syndrome is characterised by a lower motor lesion of cranial nerve VII (± VI), with a contralateral hemiplegia or hemiparesis, and the usual cause is occlusion of a pointine branch of the basilar artery. MRI is indicated.

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I have no conflict of interest regarding these questions or answers. Email: si7np5e@gmail.com

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