check

Independent learning program for GPs

Unit 557
January–February 2019

Genetics

RACGP

www.racgp.org.au/check

Subscriptions

For subscriptions and enquiries please call 1800 331 626 or email check@racgp.org.au

Published by

The Royal Australian College of General Practitioners Ltd
100 Wellington Parade
East Melbourne, Victoria 3002, Australia

Telephone 03 8699 0414
Facsimile 03 8699 0400
www.racgp.org.au

ABN 34 000 223 807
ISSN 0812-9630

We acknowledge the Traditional Custodians of the lands and seas on which we work and live, and pay our respects to Elders, past, present and future.

check
Independent learning program for GPs

Genetics

Unit 557 January–February 2019

The five domains of general practice

- Communication skills and the patient–doctor relationship
- Applied professional knowledge and skills
- Population health and the context of general practice
- Professional and ethical role
- Organisational and legal dimensions

RACGP

About this activity

As the first point of contact, general practitioners (GPs) are well placed to investigate various presentations that are suggestive of genetic disorders, coordinate long-term care and offer advice regarding genetic screening.

Cystic fibrosis (CF), affecting approximately 1 in 3700 individuals,[1] is the most common life-threatening genetic disorder in Australia.[2] It is estimated that 1 in 25 Australians are carriers of a CF genetic variant.[1]

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability, with the syndrome affecting one in 6000 females and one in 3600 males.[3] Down syndrome is the most common cause of intellectual disability overall, with the current birth rate of babies with Down syndrome in Australia being 1 in 1100.[4]

In Australia there are over 45,000 cases of the dominantly inherited disorder familial hypercholesterolaemia (FH).[5] Men with untreated FH have a >50% risk of coronary heart disease by the age of 50 years, and women have a >30% increased risk by the age of 60 years.[6] While less common, Huntington's disease affects 1 in 15,000 Australians, with a life expectancy of 15–20 years following the appearance of the first clinical symptoms.[7]

This edition of *check* considers the investigation and management of various genetic conditions in general practice.

References

1. Ahern S, Sims G, Tacey M, et al, on behalf of the Australian Cystic Fibrosis Data Registry. The Australian Cystic Fibrosis Data Registry Annual Report, 2015. Report no. 18. Melbourne: Monash University Department of Epidemiology and Preventive Medicine, 2017. Available at www.cysticfibrosis.org.au/getmedia/d0718682-f382-4a99-b6e7-f06d31d8bc36/17P-0960-Cystic-Fibrosis-Annual-Report-FINAL.pdf.aspx [Accessed 18 January 2019].
2. Delatycki MB, Burke J, Christie L, et al. Human Genetics Society of Australasia. Position statement: Population-based carrier screening for cystic fibrosis. Twin Res Hum Genet 2014;17(6):578–83.
3. Birch RC, Cohen J, Trollor JN. Fragile X-associated disorders: Don't miss them. Aust Fam Physician 2017;46(7):487–91.
4. Down Syndrome Australia. Prenatal test for Down syndrome: Fact sheet. Abbotsford, Vic: Down Syndrome Australia, [date unknown]. Available at www.downsyndrome.org.au/documents/resources/prenatal/DSA-prenatal-factsheet-C06.pdf [Accessed 18 January 2019].
5. Watts G, Sullivan D, Poplawski N, et al. Familial hypercholesterolaemia: A model of care for Australasia. Atherosclerosis 2011;12(Suppl 2):221–31.
6. The National Collaborating Centre for Primary Care. Identification and management of familial hypercholesterolaemia [database on the Internet], 2008. Available at www.nice.org.uk/nicemedia/pdf/CG071NICEGuideline.pdf [Accessed 18 January 2019].
7. Centre for Genetics Education. Huntington disease and genetic testing. St Leonards, NSW: Centre for Genetics Education, 2010. Available at www.huntingtonsnsw.org.au/sites/default/files/Huntington%20Disease%20and%20Genetic%20Testing.pdf [Accessed 18 January 2019].

Learning outcomes

At the end of this activity, participants will be able to:

- discuss the assessment and management of cystic fibrosis
- outline the management of familial hypercholesterolaemia
- summarise current recommendations for treatment of a patient who has Down syndrome
- describe the approach to diagnosing Fragile X syndrome
- identify the signs and symptoms of Huntington's disease.

Authors

David Amor (Case 4) MBBS, FRACP, PhD is Lorenzo and Pamela Galli Chair in Developmental Medicine at the University of Melbourne and a consultant clinical geneticist at Victorian Clinical Genetics Services and the Royal Children's Hospital, Melbourne. His clinical practice and research focuses on genetic causes of disability and the translation of new genetic technologies into clinical practice.

Tom Brett (Case 2) MD, MRCGP, FRACGP, MICGP, MA (Sociology) is a general practitioner and Professor and Director, General Practice and Primary Health Care Research Unit at University of Notre Dame Australia, Fremantle. His major research interests include multimorbidity, primary prevention of cardiovascular disease and familial hypercholesterolaemia. He is the lead investigator on the National Health and Medical Research Council (NHMRC) Partnership Grant 'An intervention to improve the detection and management of familial hypercholesterolaemia in primary care'.

Anne Chang (Case 1) MBBS, FRACP, MPHTM, PhD, FAPSR, FThorSoc, FAHMS is a paediatric respiratory specialist based at the Queensland Children's Hospital. She is also an NHMRC practitioner fellow based at the Centre of Children's Health Research (University of Queensland) and the Menzies School of Health Research (Darwin). She is an established clinician researcher internationally recognised for her contributions in the areas of paediatric cough, bronchiectasis and evidence-based medicine. Her major interests are in Indigenous child health, evidence-based management, airway disease, protracted bacterial bronchitis, cough and suppurative lung disease in children.

Clement Loy (Case 5) MBBS, MMed (ClinEpi), FRACP, PhD is a cognitive neurologist with an interest in molecular genetics. He is a neurologist and director of the Huntington Disease Service at Westmead Hospital, Sydney, and a clinical professor at the University of Sydney.

Elizabeth McCusker (Case 5) MBBS (Hons), FRACP is a neurologist with a commitment to clinical research in Huntington's disease. She was the founding director of the Huntington Disease Service at Westmead Hospital, and is a Clinical Associate Professor affiliated with the University of Sydney Medical School.

Dustin Mills (Case 1) MBBS(Hons I), BPharm is a paediatric respiratory fellow at the Queensland Children's Hospital. His major interests are in

Indigenous health and suppurative lung disease in children.

Paul Nguyen (Case 3) MBBS, FRACGP, DCH is a general practitioner and senior medical officer at the Centre for Developmental and Disability Health. He also works as a medical educator for Monash University and Eastern Victoria GP training. He has a special interest in mental and disability health.

Jane Tracy (Case 3) MBBS, GCHE is the Director of the Centre for Developmental Disability Health (CDDH), Monash Health, a state-wide service working to improve the health and lives of people with intellectual disability. Jane has worked clinically for over 25 years with children and adults with intellectual and associated developmental disabilities, and their families. Prior to her appointment as Director, she led the CDDH education team for many years, providing education to medical students and professional development sessions for general practitioners. She has also been involved in improving policy and practice in the healthcare of people with disability.

Peer reviewers

Lilian Downie MBBS (Hons) graduated from medical school at Monash University in Victoria, Australia in 2009 and undertook paediatric training at the Royal Children's Hospital in Melbourne in 2011. She worked for six months in general paediatrics in the Solomon Islands before commencing training in clinical genetics. Lil is currently a clinical genetics fellow at the Victorian Clinical Genetics Service, which provides comprehensive clinical and laboratory genetics services in Victoria. She is also completing her PhD through the University of Melbourne and Murdoch Children's Research Institute on the genetics of deafness and genomic newborn screening. This project is funded by the Melbourne Genomics Health Alliance in partnership with the Victorian State Government. The Alliance is a group of 10 leading healthcare and research organisations establishing systems to integrate genomics into the healthcare system in Victoria.

Chloe Stutterd BMBS, FRACP is a clinical geneticist with expertise in neurogenetics. She is a lecturer in clinical genomics and a PhD candidate at the University of Melbourne in the Department of Paediatrics.

Abbreviations

ADL	activities of daily living
AIH	Australian Immunisation Handbook
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CAG	cytosine-adenosine-guanine
CF	cystic fibrosis
cfDNA	cell-free DNA
CFRD	CF-related diabetes
cFTS	combined first-trimester screening
CFTR	cystic fibrosis transmembrane conductance regulator
CSLD	chronic suppurative lung disease
CT	computed tomography
CVD	cardiovascular disease
CVS	chorionic villus sampling
DIOS	distal intestinal obstruction syndrome
DLCN	Dutch Lipid Clinic Network
ECG	electrocardiography
FH	familial hypercholesterolaemia
FXS	Fragile X syndrome
FXTAS	Fragile X–associated tremor/ ataxia syndrome
GP	general practitioner
HD	Huntington's disease
HDL	high-density lipoprotein
IRT	immunoreactive trypsinogen
IVF	in vitro fertilisation
KSW	key support worker
LDL	low-density lipoprotein
MTDM	medical treatment decision maker
NIDDM	non–insulin-dependent diabetes mellitus
NIPT	non-invasive prenatal testing
PCR	polymerase chain reaction
PGT	preimplantation genetic testing
SMA	spinal muscular atrophy
SSA	shared supported accommodation
SSRI	selective serotonin reuptake inhibitors
VCAT	Victorian Civil and Administrative Tribunal

CASE

1 Jacquelyn has a cough

Priscilla, your long-term patient, presents with her daughter Jacquelyn, aged 12 months, who has had a persistent cough for the past five weeks. Jacquelyn was born at term weighing 3 kg. She was hospitalised three times for wheeze, which was presumed to be bronchiolitis; the first occurrence was at the age of one month. Following her last admission, aged eight months, Jacquelyn has had a chronic wet cough with intermittent wheeze. Jacquelyn has been formula fed and was thriving up until six months of age, following which her weight percentile has fallen below the third percentile. She now weighs 7.1 kg.

Question 1

What is the differential diagnosis for children with chronic cough?

Question 2

What features in Jacquelyn's history could suggest chronic suppurative lung disease (CSLD)? What further information would you elicit on history and examination if you suspected CSLD?

Further information

When you examine Jacquelyn, she has a spontaneous wet cough and localised crepitations on auscultation. She does not have any digital clubbing but looks small with little subcutaneous fat. Her weight percentiles are out of proportion to her head circumference percentile.

Question 3

What investigations would you recommend for Jacquelyn?

Further information

You request a chest X-ray, which is reported to be normal, and a nasopharyngeal swab, which is negative for both pertussis and mycoplasma polymerase chain reaction (PCR).

Jacquelyn is then referred to her local hospital, where she has a sweat test that shows an abnormal sweat chloride level (100 mmol/L; reference range <60 mmol/L). She is diagnosed with cystic fibrosis (CF) and referred to the nearest CF service, where CF transmembrane conductance regulator (*CFTR*) genetic analysis and elastase stool sample are undertaken. The stool sample shows decreased elastase, indicating pancreatic insufficiency. Jacquelyn's family is referred to a genetic counsellor.

Question 4

Priscilla has not yet completed her family, and would like to know about the likelihood of future children being affected by CF. What can you tell her about this?

Question 5

How common is CF in Australia?

Question 6

Priscilla asks why the CF was not identified by Jacquelyn's neonatal heel prick test. How accurate are these tests?

Question 7

What are the possible clinical presentations of undiagnosed CF?

Question 8

What can you tell Priscilla about Jacquelyn's long-term prognosis? What is the current life expectancy of a child born with CF?

Further information

At the age of three years, Jacquelyn presents to you with acute colic-like abdominal pain, and Priscilla reports that in recent hours Jacquelyn has developed abdominal distension and is refusing oral intake.

Question 9

What CF-related diagnosis do you need to consider? What will your management be?

Further information

At your next appointment you assess Jacquelyn's height and weight, and note that her body mass index (BMI) is now below the fifth percentile.

Question 10

What is Jacquelyn's target BMI? How can you, as Jacquelyn's general practitioner (GP), contribute to optimising her nutritional status?

Question 11

What additional immunisations does Jacquelyn require?

Further information

Jacquelyn is commenced on ivacaftor, a *CFTR* modulator, by her CF team.

Question 12

What is the role of *CFTR* modulators?

CASE 1 Answers

Answer 1

Chronic cough in children is defined as a daily cough of >4 weeks' duration. Most acute respiratory infections in children resolve within this interval.[1] Chronic cough should be systematically assessed as it may represent sinister underlying aetiologies.[2] Specific cough refers to a chronic cough attributable to a pathological cause, while non-specific cough is a dry cough with the absence of cough pointers that typically resolves gradually.[2]

In Australia, the most common cause of chronic wet cough in children referred to specialists is protracted bacterial bronchitis, and the most common cause of dry cough is non-specific cough.[2] There are many causes of chronic cough, including:

- asthma-associated cough (where other symptoms are present)
- non-specific cough
- protracted bacterial bronchitis
- controversial (post-nasal drip, eg from allergic rhinitis, chronic sinusitis)
- CSDLs such as CF and bronchiectasis (from primary ciliary dyskinesia, immunodeficiency, post-infections, etc)
- foreign body aspiration
- post-pertussis cough
- airway structural anomalies (eg trachea-oesophageal fistula, tracheobronochomalacia)
- interstitial lung disease (eg autoimmune, bronchiolitis obliterans)
- recurrent aspiration in children with neurological disorders
- non-respiratory causes such as cardiac causes (eg pulmonary oedema, arrhythmia), medications (eg angiotensin-converting enzyme inhibitors) or psychogenic/habit cough.[3]

Answer 2

In Jacquelyn, two features that suggest the presence of CSLD are recurrent severe respiratory infections and growth failure (ie falling weight percentiles). Other main features on history that may signify CSLD in children include chronic wet cough (not responding to four weeks of antibiotics), recurrent wheeze and features of underlying aetiology for CSLD including symptom onset from early life and, sometimes, a family history.[4] Haemoptysis is a rare presenting symptom in children in mainstream Australian settings. In infants, although wheeze is typically caused by viral infections, it can also be associated with CSLD and other chronic diseases.

Examination findings suggestive of CSLD include digital clubbing, chest wall abnormalities (eg hyperinflation, Harrison's sulci), auscultatory crackles and a 'wasted'

appearance. Other features that may be suggestive of an underlying disease include hepatomegaly with or without splenomegaly (which indicate CF-related liver disease or rare metabolic diseases but are rare at Jacqueline's age), situs inversus (suggestive of primary ciliary dyskinesia) and skin rashes (immune dysregulation disorder).[5]

Answer 3

All children with chronic cough should have chest radiography and spirometry performed when age-appropriate;[6] most children aged >6 years can perform spirometry reliably.[7] Abnormality in either chest radiography or spirometry indicates the presence of specific cough; however, when the test results are normal, neither specific cough nor absence of disease are excluded.[1] Other investigations are governed by history and clinical examination. Nasopharyngeal swab PCR for mycoplasma and pertussis may be indicated.

A child's presentation and/or investigations may necessitate discussion with a paediatrician or paediatric respiratory physician depending on local resources. Jacqueline has three features suggesting specific cough (ie wet cough, recurrent hospitalisations, growth failure), which warrants specialist involvement.

Answer 4

CF is an autosomal recessive condition caused by variants (mutations) in both copies of the *CFTR* gene, one inherited from each parent. When both parents are carriers of a CF gene variant, there is a one in four chance that their child will inherit two abnormal CF gene variants and so will have CF, a one in two chance their child will be a carrier of a CF variant only, and a one in four chance their child will neither have CF nor be a carrier of a CF variant. Prenatal testing and pre-implantation genetic diagnosis for CF may be offered to known CF carriers. CF carrier testing is available to couples in Australia;[8] however, this may incur an out-of-pocket cost. Families should also be aware that carrier testing only detects the most common variants causing CF in the Australian population and therefore may not detect carrier status in ethnic minorities.[9,10]

Answer 5

CF is the most common life-shortening autosomal recessive disease among Caucasian populations, with a frequency of approximately 1 in 2500 live births.[10] CF is caused by mutations in a single large gene on chromosome 7 that encodes the CFTR protein, a complex chloride channel and regulatory protein found in all exocrine tissues. Deranged transport of chloride and/or other CFTR-affected ions, such as sodium and bicarbonate, leads to thick, viscous secretions in the lungs, pancreas, liver, intestine and reproductive tract, and to increased salt content in sweat gland secretions.[9] There are currently 2030 variants listed in the *CFTR* variant database, of which 120 are responsible for the vast majority of disease cases.[11]

The prevalence of the CF gene variants varies among ethnicities. The highest carrier frequency (1 in 25) occurs in Caucasians, and a lower rate (1 in 160) among South East Asians.[12] The incidence of CF is rare in Aboriginal and Torres Strait Islander peoples. The 2016 Australian CF registry reported that the most common genotypes were homozygous *F508del* (47.0%), *F508del* in combination with another variant (40.9%; compound heterozygous), and then other variants (7.4%).[13]

Answer 6

Newborn screening for CF is universal in Australia, but each state has slightly different protocols. Screening typically employs two steps: heel prick immunoreactive trypsinogen (IRT), followed by DNA analysis for *CFTR* variants if IRT is elevated. Currently, in Queensland, an abnormal IRT is followed by a DNA analysis for 50 *CFTR* variants. IRT is a precursor to trypsin that is elevated cases of CF with pancreatic dysfunction. The initial IRT test is approximately 80% sensitive for detecting CF;[14] therefore, some cases of CF will be missed by the newborn screen.

The 2016 Australian Cystic Fibrosis Data Registry reported 73 new diagnoses of CF; 55 (75%) of these were diagnosed in early infancy, and the remainder (25%) were identified later based on clinical recognition followed by confirmatory tests.[13] Of those diagnosed in early infancy, approximately 60% were diagnosed on neonatal screening, 6% identified following meconium ileus, 4% with genetic testing in the context of a CF-affected sibling and 6% with prenatal diagnosis. Of those diagnosed at a later stage, two were diagnosed in early childhood (aged 1–4 years), three when aged 5–9 years and four as adults.[13]

Answer 7

The onset of clinical symptoms varies widely and is somewhat related to *CFTR* genotype, with a spectrum from focal male reproductive tract involvement (congenital absence of the vas deferens) to multi-organ involvement in classic CF. Most patients (85–90%) with CF have pancreatic exocrine insufficiency and progressive suppurative lung disease (classical CF).[15] Typical respiratory manifestations include a persistent, productive cough; hyperinflation of the lung fields on chest radiography; and pulmonary function tests that are consistent with obstructive airway disease.[15] The majority of patients with CF develop sinus disease. Nasal polyposis is seen in 10–32% of patients.[16]

Insufficiency of the exocrine pancreas is present from birth in approximately 66% of patients with CF. An additional 20–25% develop pancreatic insufficiency during the first years of life.[17] Common symptoms and signs of pancreatic insufficiency include steatorrhea (frequent, bulky, foul-smelling oily stools) and growth failure due to fat malabsorption (as in the case of Jacqueline). Rectal prolapse now occurs rarely in children with CF.[13]

Meconium ileus is characterised by obstruction of the bowel by meconium in a newborn infant. It is the presenting problem in 10–20% of newborns with CF.[18] Conversely, 80–90% of infants with meconium ileus have CF.[18]

Patients diagnosed in adulthood are more likely than children

to present with gastrointestinal symptoms, diabetes mellitus and infertility. These adults are more likely than children to have rare genetic variants rather than the common known variants, normal pancreatic function and equivocal sweat chloride results.[15] Patients with CF may also present with hyponatraemic dehydration in the context of elevated sweat sodium loss.[15]

Answer 8

The 2017 UK CF registry estimated the median survival of patients with CF to be age 47 years; that is, 50% of children with CF born in 2017 are predicted to live to at least 47 years of age.[19] There has been a marked increase in the survival of people with CF in recent decades, largely due to earlier diagnosis, the optimisation of nutrition, and pulmonary health in patients with CF (prior to the availability of *CFTR* modulators). The improved survival rate has led to a change in the demographics of the CF population, such that the mean age of the Australian CF registry population on 31 December 2016 was 21.5 years, and there are now more adults with CF than children.[13] The recent availability of *CFTR* modulators is expected to further contribute significantly to the increased survival of patients with CF. While fertility may be reduced, most women with CF are able to conceive naturally. Over 95% of men with CF are infertile because of defects in sperm transport (ie obstructive azoospermia).[20] Most of these men have congenital bilateral absence of the vas deferens. Dysfunction and/or absence of the seminal vesicles accounts for low-volume ejaculate.[20] However, active spermatogenesis occurs within the testis, and sexual function is not primarily affected.[20] Reproductive technologies can permit affected men to become biological fathers. Early discussion regarding sexual and reproductive health is important in patients with CF.

The routine care needs of a child with CF are team-based with input from paediatric respiratory specialists, nurses, physiotherapists, dieticians and, on occasion, clinical psychologists, occupational therapists, social workers, pharmacists and other medical specialists (eg endocrinologists specialising in CF-related diabetes). Most guidelines recommend four CF clinic visits per year, including one comprehensive annual visit and three visits to review growth and nutrition and respiratory status (including lung function – spirometry typically from age five to six years). Although different CF centres will have their own guidelines, annual screening investigations in CF would typically include full blood count; electrolytes and liver function tests; vitamin A, E and D; coagulation profile and aspergillus profile. Oral glucose tolerance tests are typically commenced when the child is aged >10 years. Screening imaging may include ultrasonography of liver and spleen for CF-related liver disease in children aged ≥5 years on alternate years (or annually if abnormal); bone densitometry (dual-energy X-ray absorptiometry scans) from 10 years of age every 1–3 years, or annually if abnormal; respiratory sample (sputum or cough swab) for microbiology, including assessment for non-tuberculous mycobacteria, is sought periodically, while some children may require a bronchioalveolar lavage. In addition to lung function testing, lung imaging with chest X-ray or high resolution computed tomography may be required.[21]

Treatment guidelines for respiratory medications in CF recommend a number of chronic maintenance treatments including bronchodilators, mucolytics, inhaled antibiotics, anti-inflammatories and airway hydrators. In addition, a vigorous airway clearance regimen and regular exercise are recommended for most patients with CF. This treatment regimen is both time-consuming and complex, requiring use of specific devices, such as inhalers or nebulisers, with varying administration and cleaning times. Beyond pulmonary care, most individuals with CF require additional therapies, such as pancreatic enzyme replacement and/or nutritional supplements. Some patients with CF have the additional burden of central venous access devices or feeding devices such as nasogastric tubes or percutaneous gastrostomy tubes. As a result, the treatment burden for patients with CF is high, with estimates suggesting the regimen takes 2–3 hours per day for routine CF care.[21] Consequently, adherence to CF treatment regimens is often poor, generally ≤50% to prescribed therapies.[22]

Answer 9

Jacquelyn may have distal intestinal obstruction syndrome (DIOS) and should be referred to her nearest emergency department. DIOS is an acute complete or incomplete obstruction of the small intestine, most commonly the ileocecum, by intestinal contents that have been thickened by dehydration, or 'inspissated'. The pathogenesis of DIOS is not fully understood.[23] Risk factors for developing DIOS include certain genotypes (eg *F508del*), pancreatic insufficiency, poorly controlled fat malabsorption, dehydration, and prior episodes of DIOS.[24] DIOS is unique to CF and occurs in 10–50% of patients at any age.[25] The most common manifestation of DIOS is colicky abdominal pain. The onset of symptoms can be acute or intermittent, and the symptoms tend to become progressively severe over time. Other features include abdominal distension, flatulence, weight loss and poor appetite.[24] Vomiting may ensue when complete obstruction develops. Patients usually are constipated but also may have diarrhoea or even a normal stool pattern. On examination, faecal mass may be palpable. Abdominal X-ray typically reveals accumulation of stool in the distal small intestine and right colon; the stool is typically 'bubbly' in appearance.[26] Air fluid levels and small bowel dilatation may be seen with complete obstruction. Management focuses on correcting fluid and electrolyte abnormalities, if present, and removing the inspissated plug using osmotic laxatives. Surgery is rarely required.[24]

Answer 10

People with CF frequently have growth failure caused by a combination of malabsorption, increased energy needs and reduced appetite. To address this risk, the target weight ranges for children affected by CF are higher. The 2017 Australia and New Zealand CF Nutrition Guidelines suggest the following targets: children aged 0–24 months aim for a weight for length >50th percentile (using World Health Organization growth charts), and those aged 2–18 years aim

for a BMI between the 50–85th percentiles (Centres for Disease Control and Prevention growth charts).[27] Another important indicator of nutritional sufficiency is the achievement of full genetic potential for height as indicated by mid-parental height range.

Early recognition and intensive treatment of undernutrition in patients with CF can minimise the effects of malnutrition on lung disease, longevity and quality of life.[28] If not corrected, undernutrition may result in altered pulmonary defence mechanisms, altered pulmonary muscle function, decreased exercise tolerance, immunology impairment, growth defects and inadequate accretion of bone mineral.[29]

GPs have a key role in supporting patients with CF to achieve nutrition targets by highlighting the benefits of good nutrition and the risks of undernutrition, as well as supporting behavioural change in patients with CF who are not meeting nutritional goals. In particular, patients benefit from appropriate dosing of pancreatic enzymes (when pancreatic insufficient) and adherence with fat-soluble vitamin supplementation and high salt intake. Nutritional supplements via the oral or enteral route may ultimately be required to meet nutritional goals. GPs should also be vigilant for the development of CF-related diabetes (CFRD), which can cause nutritional decline. CF centres would typically screen for CFRD with an annual oral glucose tolerance test from age 10 years.

Answer 11

The Australian Immunisation Handbook (AIH) recommends an annual influenza vaccine in people with chronic respiratory conditions.[30] Viral respiratory infections cause exacerbations of respiratory issues, and children with CF are at an increased risk of influenza, which may cause irreversible loss of lung function.[31]

Although *Streptococcus pneumoniae* is not a major cause of pulmonary exacerbations in CF, the AIH recommends additional pneumococcal vaccinations at six months and four years of age. In combination with the usual vaccination schedule, this is a total of four infant doses of 13vPCV (two, four, six and 12 months of age) and 23vPPV at four years of age (repeated 10 years later).[30]

Answer 12

CFTR modulators act by improving production, intracellular processing, and/or function of the defective CFTR protein. The indications and efficacy of these drugs depend upon the *CFTR* variant in the individual patient, and therefore all patients with CF should undergo CF genotyping. There are now several *CFTR* modulators available under the pharmaceutical benefits scheme. Ivacaftor is an oral medication that acts as a potent and selective *CFTR* potentiator that increases the chloride ion transport properties of the channel.[32] Studies have shown the efficacy of ivacaftor, with significant reduction in pulmonary exacerbations and improved respiratory symptoms, weight and lung function in these genotype-specific patients.[9,10]

Resources for health professionals

- Genetics Home Reference; Cystic fibrosis, https://ghr.nlm.nih.gov/condition/cystic-fibrosis
- Women's and Children's Hospital; Nutrition for medical conditions – Cystic fibrosis, www.wch.sa.gov.au/services/az/other/nutrition/cystic_fibrosis.html
- Castellani C, Duff AJA, Bell SC, et al. ECFS best practice guidelines: The 2018 revision. J Cyst Fibros 2018;17(2):153–78. doi: 10.1016/j.jcf.2018.02.006.
- Cystic Fibrosis Foundation; Clinical care guidelines, www.cff.org/Care/Clinical-Care-Guidelines
- Villanueva G, Marceniuk G, Murphy MS. Diagnosis and management of cystic fibrosis: Summary of NICE guidance. BMJ 2017;359:j4574. doi: 10.1136/bmj.j4574.

Resources for patients

- Cystic Fibrosis Australia, www.cysticfibrosis.org.au/
- Donnelley M, Parsons D. Explainer: What is cystic fibrosis and how is it treated? The Conversation. 27 September 2016. http://theconversation.com/explainer-what-is-cystic-fibrosis-and-how-is-it-treated-59681
- Victoria State Government; BetterHealth Channel – Cystic fibrosis (CF), www.betterhealth.vic.gov.au/health/conditionsandtreatments/cystic-fibrosis-cf

References

1. Chang AB, Oppenheimer JJ, Weinberger MM, et al. Use of management pathways or algorithms in children with chronic cough: CHEST Guideline and Expert Panel Report. Chest 2017;151(4):875–83. doi: 10.1016/j.chest.2016.12.025.
2. Chang AB, Robertson CF, Van Asperen PP, et al. A multicenter study on chronic cough in children: Burden and etiologies based on a standardized management pathway. Chest 2012;142(4):943–50. doi: 10.1378/chest.11-2725.
3. Chang AB, Oppenheimer JJ, Weinberger M, et al. Etiologies of chronic cough in paediatric cohorts: CHEST Guideline and Expert Panel Report. Chest 2017;152(3):607–17. doi: 10.1016/j.chest.2017.06.006.
4. Goyal V, Grimwood K, Marchant JM, Masters IB, Chang AB. Bronchiectasis in children: No longer an orphan disease. Pediatr Pulmonol 2016;51(5):450–69. doi: 10.1002/ppul.23380.
5. Chang AB, Bush A, Grimwood K. Bronchiectasis in children: Diagnosis and treatment. Lancet 201;392(10150):866–79. doi: 10.1016/S0140-6736(18)31554-X.
6. Chang AB, Marchant JM. Approach to chronic cough in children. In: Mallory G, editor. Waltham, MA: UpToDate, 2018.
7. National Asthma Council Australia. Australian Asthma Handbook v1.3. South Melbourne, Vic: National Asthma Council Australia, 2017. Available at www.asthmahandbook.org.au [Accessed 2 November 2018].
8. HGSA/RANZCOG Joint Committee on Prenatal Diagnosis and Screening. Prenatal screening and diagnosis of chromosomal and genetic conditions in the fetus in pregnancy. Melbourne: RANZCOG, 2015. Available at www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Prenatal-screening-and-diagnosis-of-chromosomal-and-genetic-conditions-(C-Obs-59)-Amended-May-2016.pdf?ext=.pdf [Accessed 13 January 2019].

9. Elborn JS. Cystic fibrosis. Lancet 2016;388(10059):2519–31. doi: 10.1016/S0140-6736(16)00576-6.
10. Ratjen F, Bell SC, Rowe SM, Goss CH, Quittner AL, Bush A. Cystic fibrosis. Nat Rev Dis Primers 2015;1:15010. doi: 10.1038/nrdp.2015.10.
11. CFTR2 Team. The Clinical and Functional Translation of CFTR (CFTR2). Baltimore, MD: Johns Hopkins University, 2011. Available at http://cftr2.org [Accessed 2 November 2018].
12. Human Genetics Society of Australasia Genetic Services Committee. Population Based Carrier Screening for Cystic Fibrosis. Alexandria, NSW: Human Genetics Society of Australasia, 2013. Available at www.hgsa.org.au/documents/item/1282 [Accessed 2 November 2018].
13. Australian Cystic Fibrosis Data Registry. The Australian Cystic Fibrosis Data Registry Annual Report, 2016. Report no. 19. Melbourne: Monash University, 2018. Available at www.cysticfibrosis.org.au/dataregistry [Accessed 2 November 2018].
14. Fritz A. Estimating the annual number of false negative cystic fibrosis newborn screening. Pediatr Pulmonol 2012;47(2):207–08. doi: 10.1002/ppul.21561.
15. Katkin JP. Cystic fibrosis: Clinical manifestations and diagnosis. In: Mallory G, editor. Waltham, MA: UpToDate, 2018.
16. Yung MW, Gould J, Upton GJ. Nasal polyposis in children with cystic fibrosis: A long-term follow-up study. Ann Otol Rhinol Laryngol 2002;111(12 Pt 1):1081–06.
17. Pillarisetti N, Williamson E, Linnane B, et al. Infection, inflammation, and lung function decline in infants with cystic fibrosis. Am J Respir Crit Care Med 2011;184(1):75–81. doi: 10.1164/rccm.201011-1892OC.
18. Fakhoury K, Durie P, Levison H, Canny G. Meconium ileus in the absence of cystic fibrosis. Arc Dis Child 1992;67(10 Spec No):1204–06.
19. Cystic Fibrosis Trust UK. Cystic Fibrosis Registry 2017 Annual Data Report. London: CFT, 2017. Available at www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources [Accessed 2 November 2018].
20. Sawyer SM, Farrant B, Cerritelli B, Wilson J. A survey of sexual and reproductive health in men with cystic fibrosis: New challenges for adolescent and adult services. Thorax 2005;60:326–30. doi: 10.1136/thx.2004.027599.
21. Sawicki GS1, Ren CL, Konstan MW, et al. Treatment complexity in cystic fibrosis: Trends over time and associations with site-specific outcomes. J Cyst Fibros 2013;12(5):461–67. doi: 10.1016/j.jcf.2012.12.009.
22. Modi AC, Lim CS, Yu N, Geller D, Wagner MH, Quittner AL. A multi-method assessment of treatment adherence for children with cystic fibrosis. J Cyst Fibros 2006;5(3):177–85.
23. Houwen RH, van der Doef HP, Sermet I, et al. Defining DIOS and constipation in cystic fibrosis with a multicentre study on the incidence, characteristics, and treatment of DIOS. J Pediatr Gastroenterol Nutr 2010;50(1):38–42. doi: 10.1097/MPG.0b013e3181a6e01d.
24. Colombo C, Ellemunter H, Houwen R, et al. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. J Cyst Fibros 2011;10 Suppl 2:S24–8. doi: 10.1016/S1569-1993(11)60005-2.
25. Dray X, Bienvenu T, Desmazes-Dufeu N, Dusser D, Marteau P, Hubert D. Distal intestinal obstruction syndrome in adults with cystic fibrosis. Clin Gastroenterol Hepatol 2004;2(6):498–503.
26. Lin LY, Wong JU. Images in clinical medicine. Meconium-like ileus in cystic fibrosis. N Engl J Med 2012;366(21):2017. doi: 10.1056/NEJMicm1112678.
27. Thoracic Society of Australia and New Zealand. Nutrition guidelines for cystic fibrosis in Australia and New Zealand. Sydney: Thoracic Society of Australia and New Zealand, 2017. Available at www.clinicalguidelines.gov.au/portal/2584/nutrition-guidelines-cystic-fibrosis-australia-and-new-zealand [Accessed 2 November 2018]
28. Peterson ML, Jacobs DR Jr, Milla CE. Longitudinal changes in growth parameters are correlated with changes in pulmonary function in children with cystic fibrosis. Pediatrics 2003;112(3 Pt 1):588–92.
29. Turck D, Braegger CP, Colombo C, et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. Clin Nutr. 2016;35(3):557–77. doi: 10.1016/j.clnu.2016.03.004.
30. Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook. Canberra: DoH, 2018. Available at https://immunisationhandbook.health.gov.au [Accessed 2 November 2018].
31. Viviani L, Assael BM, Kerem E, ECFS (A) H1N1 study group. Impact of the A (H1N1) pandemic influenza (season 2009–2010) on patients with cystic fibrosis. J Cyst Fibros 2011;10(5):370–06. doi: 10.1016/j.jcf.2011.06.004.
32. Vertex Pharmaceuticals Incorporated. Manufacturer's prescribing information for Kalydeco (ivacaftor) tablets. Boston, MA: Vertex Pharmaceuticals Incorporated, 2018. Available at http://pi.vrtx.com/files/uspi_ivacaftor.pdf [Accessed 31 October 2018].

CASE

2 Zehra has vague chest discomfort

Zehra, an accountant aged 41 years, presents after experiencing vague chest discomfort while walking uphill five days ago. Zehra is concerned by this symptom because her father, a non-smoker who exercised regularly and was not overweight, had died suddenly from a heart attack aged 53 years.

Question 1

What assessment will you undertake?

Further information

Zehra describes heaviness centrally in her chest, which came on after walking 200 m uphill. There was some associated breathlessness but no nausea or light-headedness. There was no radiation or diaphoresis. Her discomfort resolved after resting for a few minutes. This is the first time she has experienced this discomfort. She was not aware of any acid reflux and had not recently eaten a meal.

Zehra has never smoked, attends the gym twice a week, walks regularly and drinks two glasses of wine at weekends. She attributed the chest discomfort to 'indigestion'.

You take a broader family history and discover that Zehra's paternal grandmother, who was of Lebanese origin, had a heart attack at the age of 52 years and died aged 62 years. Her father's two younger sisters live overseas in Europe and she sees them infrequently; she thinks one of them takes cholesterol-lowering medication. On her mother's side, both of Zehra's grandparents lived into their 70s and, apart from maturity-onset diabetes in her grandmother, there are no known heart problems. Her mother is fit and well, aged 69 years. Zehra has two brothers, aged 40 and 46 years; she is not aware of anything sinister in their medical histories. Her husband is aged 42 years and they have two children, a boy aged eight years and a girl aged nine years.

On examination, Zehra's blood pressure is 115/75 mmHg and body mass index (BMI) is 24.5 kg/m^2. Physical examination including chest and cardiovascular systems are normal. Electrocardiography (ECG) confirms sinus rhythm at 76 beats/min, and there are no ischaemic changes.

You arrange an immediate non-fasted lipid profile test and random glucose for Zehra at the practice and book an exercise stress ECG. As Zehra is stable, more invasive testing is not considered at this stage.

Lipid profile reveals total cholesterol of 7.3 mmol/L (reference range <5.5 mmol/L); high-density lipoprotein (HDL) cholesterol level of 1.9 mmol/L (reference range >1.0 mmol/L); low-density lipoprotein (LDL) cholesterol level of 5.0 mmol/L (reference range <3.0 mmol/L), and triglyceride level of 0.9 mmol/L (reference range <1.8 mmol/L). The random glucose is normal.

The exercise stress ECG is reported as negative for inducible myocardial ischaemia.

Question 2

What are your differential diagnoses?

Question 3

What additional investigations would help to clarify the diagnosis at this stage?

Further information

The fasting lipids are comparable to earlier levels, while liver, renal (including macroproteinuria) and thyroid functions are all reported as being within normal limits. Her fasting glucose levels are normal. No physical stigmata of familial hypercholesterolaemia (FH) are found.

Question 4

What do the results and family history suggest?

Further information

Zehra is taken aback at the prospect of medication for her newly discovered high cholesterol levels and wonders if she could trial diet and exercise for a few months. In addition, some of her friends have used statins in the past but stopped after hearing 'bad reports' about them in the media.

A review of Zehra's diet and lifestyle shows low amounts of saturated fats and cholesterol, low alcohol intake, and consumption of fresh fruits, vegetables, chicken, fish and mostly lean meats. You know from your initial consultation that Zehra is a non-smoker and exercises regularly.

Question 5

What do you advise Zehra regarding medications and diet?

Question 6

How would you proceed with confirming your diagnosis of FH? How would you commence management of the condition?

Further information

The repeat lipids after a month on the statin reveal total cholesterol of 4.5 mmol/L (reference range <5.5 mmol/L); HDL cholesterol level of 1.8 mmol/L (reference range >1.0 mmol/L); LDL cholesterol level of 2.3 mmol/L (reference range <3.0 mmol/L), and triglyceride level of 0.9 mmol/L (reference range <1.8 mmol/L). Zehra reported no muscle aches and tolerated the statin well.

The specialist agreed FH was likely and counselled Zehra to undertake genetic testing, which confirmed deletion in the LDL receptor (*LDLR*) gene, adding 8 to her Dutch Lipid Clinic Network (DLCN) score (Table 1). This extra information strengthened the need for cascade testing among close relatives.

Question 7

What information can you give Zehra about FH?

Question 8

Zehra asks whether her family members should be tested for FH. What would you advise her?

Further information

Zehra contacted her two brothers and advised them that her general practitioner (GP) and specialist both agreed she had inherited FH and suggested they should be tested also. Her brother Fahd, aged 46 years, had normal cholesterol levels. Her other brother, Amir, aged 40 years, showed total

cholesterol of 8.9 mmol/L (reference range <5.5 mmol/L); HDL cholesterol level of 1.9 mmol/L (reference range >1.0 mmol/L); LDL-cholesterol level of 6.4 mmol/L (reference range <3.0 mmol/L), and triglyceride level of 1.4 mmol/L (reference range <1.8 mmol/L). Amir was subsequently seen at the lipid disorders clinic and genetic testing confirmed he too had a deletion on his *LDLR* gene. His two daughters and son have now been offered testing for FH. A family pedigree is shown in Figure 1.

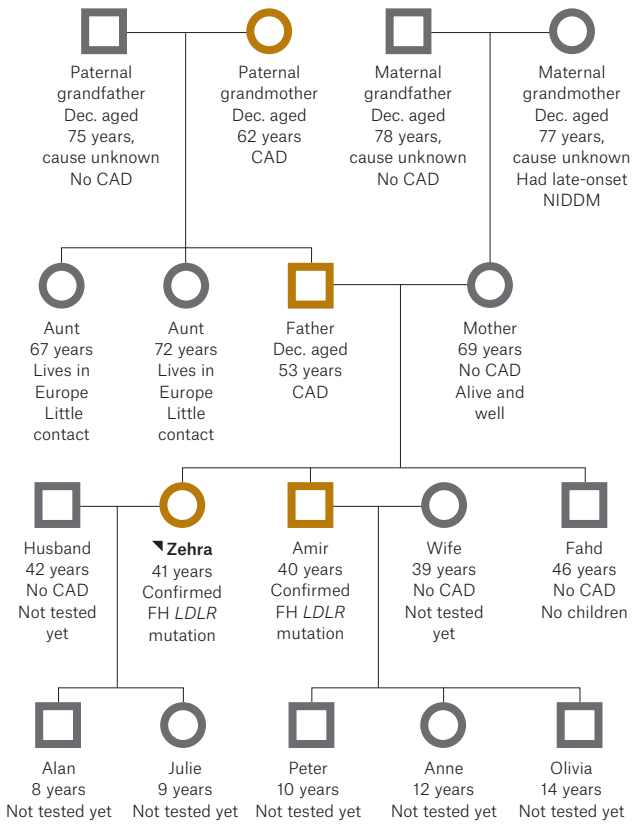

Figure 1. Zehra's family pedigree; colour indicates diagnosed or suspected familial hypercholesterolaemia.

CAD; coronary artery disease; FH, familial hypercholesterolaemia; NIDDM, non-insulin-dependent diabetes mellitus

Question 9

What prognosis can you offer patients with FH? How can we improve awareness of FH?

Question 10

How should follow-up be managed?

CASE 2 Answers

Answer 1

Initial evaluation should include a detailed history of the presenting symptom as well as a personal, family and social history. You should also assess BP and BMI and perform a chest examination. You should also perform ECG.

Answer 2

Zehra's history of chest discomfort raises the possibility of early angina pectoris, especially in a young woman with a family history. The abnormal lipid profile and family history raise the possibility of FH. Other possible explanations for her elevated cholesterol levels could include diabetes mellitus, hypothyroidism, and liver or renal diseases (such as cholestasis, chronic kidney disease, or nephrotic syndrome).[1,2]

Answer 3

The elevated cholesterol levels should prompt you to order extra blood tests to include fasting glucose, liver, renal and thyroid function tests, repeat lipids (fasting) and creatine kinase.[3]

You should undertake a focused examination to check for potential physical stigmata of FH (tendon xanthomata, arcus cornealis) or hypercholesterolaemia (xanthelasma).[1,4]

Answer 4

Zehra's family history, especially the presence of premature coronary artery disease (CAD) in her father and paternal grandmother, and her high LDL level indicate the possibility of FH[1,5] and early atherosclerosis causing angina. Further evaluation and drug treatment with lipid-lowering medications (statins)[4,6–8] should be considered.

One tool for diagnosis of FH is the DLCN diagnostic criteria (Table 1). Applying the phenotypic criteria, Zehra has a DLCN

score[9] of 3 for her LDL cholesterol of 5.0 mmol/L and a further 1 for her father's premature CAD, yielding a score of 4. If her chest discomfort was angina, this would yield a further score of 2 for personal premature CAD. Her total DLCN score would therefore be 6, satisfying the phenotypic criteria for 'probable' FH.

Answer 5

Overall, Zehra has a balanced diet and lifestyle. You explain that you suspect the cause for her elevated cholesterol is a hereditary condition, which carries a far higher risk of complications, as the cholesterol burden begins from birth and increases progressively with time if not purposefully managed.[1,2,6] Of particular concern is the possibility of angina as a cause for her chest discomfort. The possibility of atherosclerosis developing is real, and if she has FH, the cholesterol burden has been present for 41 years. In this setting, diet and exercise alone would not be sufficient to reduce her risk of complications; statins are the mainstay of treatment.[1,4,6–8,10,11]

You explain to Zehra that the evidence supporting the use of statins to prevent cardiovascular disease in patients at high risk is well established.[12] Recent controversies have surrounded the use of statins in people with raised cholesterol but low overall risk of cardiovascular disease, where the benefit may be much smaller. All medications can have side effects, and a small proportion of patients experience statin-related muscle aches, pain or weakness, as well as a small increase in the risk of diabetes.[11,13] You are able to reassure her that statins are generally well tolerated, and the rate of statin intolerance is low, particularly in the absence of pre-existing comorbidities.[12,14]

Overall, successful long-term survival, reduced risk of CAD and prevention of atherosclerosis progression are positive indicators for the immediate introduction of medications.[4,6–8]

Answer 6

At this point it would be recommended that Zehra commence treatment with a high-intensity statin (rosuvastatin 20 mg daily)[15] together with ongoing low-fat diet and regular exercise.[1,4,6–8,10] Given the suspicion of FH, Zehra should be referred for specialist assessment for consideration of genetic testing and 'cascade testing' of relatives. Lipid-modifying therapy in FH follows the same principles as in other forms of hypercholesterolaemia, but combination therapy is more frequently required.[12]

Most capital cities in Australia have lipid specialists with an interest in FH, with dedicated lipid disorders clinics currently operating in Sydney, Melbourne, Brisbane, Adelaide and Perth. Testing of fasting lipids should be repeated prior to specialist appointment.

Answer 7

FH is a genetic condition associated with a defect in the LDL cholesterol receptor. It is an autosomal dominant condition with very high penetrance.

Table 1. Dutch Lipid Clinic Network criteria for making a diagnosis of familial hypercholestrolaemia in adults

	Score
Family history	
First-degree relative with known premature coronary and/or vascular disease (men aged <55 years and women aged <60 years) or First-degree relative with known low-density lipoprotein-cholesterol (LDL-C) above the 95th percentile for age and sex	1
First-degree relative with tendinous xanthomata and/or arcus cornealis or Children aged <18 years with LDL-C above the 95th percentile for age and sex	2
Clinical history	
Patient with premature coronary artery disease (ages as above)	2
Patient with premature cerebral or peripheral vascular disease (as above)	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to 45 years of age	4
LDL-C (mmol/L)	
LDL-C ≥8.5	8
LDL-C 6.5–8.4	5
LDL-C 5.0–6.4	3
LDL-C 4.0–4.9	1
Deoxyribonucleic acid (DNA) analysis: functional mutation in the low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*APOB*) or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene	8
Stratification	**Total score**
Definite familial hypercholesterolaemia (FH)	≥8
Probable FH	6–7
Possible FH	3–5
Unlikely FH	<3

Reproduced with permission from Elsevier from Watts GF, Sullivan DR, Poplawski N, et al. Familial Hypercholesterolaemia Australasia Network Consensus Group (Australian Atherosclerosis Society). Familial hypercholesterolaemia: A model of care for Australasia. Atheroscler Suppl 2011;12(2):221–63.

Unfortunately, public and professional awareness of FH is very low and the condition is often underdiagnosed. The prevalence of FH in the general community is 1 in 250 (0.4%); currently only 1–5% of affected patients are being diagnosed in Australia.[16] It was previously thought that the incidence was about half that (1 in 500). In communities with a founder effect[1,2] – for example, Afrikaans in South Africa, French

Canadians and Lebanese Christians – the incidence is higher still. These figures refer to the heterozygous form of FH where the gene variant is present only on one copy of the gene (allele). The homozygous form of FH occurs when both copies of the gene have the variant;[5] approximately 1 in 300,000 in the general community are affected. Homozygous FH is a much more aggressive and lethal disorder in affected individuals.[1,4,5]

FH meets all the World Health Organization criteria for a worthwhile screening program.[1,4,6,10] The relatively long latent period before the onset of premature CAD[8] provides the ideal opportunity to introduce effective drug and lifestyle changes. Primary care is ideally placed to undertake detection and treatment. Specialist help should be sought for more complex, hard-to-manage patients as well as for children and pregnant women.[1,2,4,17] Specialist help should also be sought if the GP needs support and reassurance in establishing the diagnosis of FH and in ongoing management.

Because FH is hereditary and present from birth, the lifetime cholesterol burden progressively accumulates, making the relative risk from FH very high and the use of absolute cardiovascular disease (CVD) risk calculators[18] inappropriate and to be avoided.[1,2,4,10,11,19,20] The UK National Institute for Health and Care Excellence guidelines[15] similarly highlight coronary heart disease risk estimation tools, based on the Framingham algorithm, as unsuitable in such patients.

Scientists have known about FH for many years, but the discovery in 1973 by Brown and Goldstein that the underlying genetic flaw causing FH in affected individuals was due to defect in the LDL cholesterol receptor helped revolutionise our understanding and knowledge of cholesterol metabolism.[21] It paved the way for dramatic advances in the treatment of cholesterol-linked diseases and led to them being awarded the Nobel Prize for Medicine in 1985.

Answer 8

As a result of the hereditary nature of FH,[5,10,22] all first-degree relatives (parents, siblings and children) of a diagnosed individual have a 50% chance of having the disorder. Cascade testing[1,6,23–26] refers to an evidence-based process for detecting high-risk genetic disorders in families. It is a cost-effective and efficient[23,26] approach to diagnose those most at risk. A family pedigree should be taken and those at risk identified. If the index case has a causative genetic variant identified, those at risk can be offered testing. A medical evaluation of the at-risk relatives is warranted, as identification of the genetic variant in isolation does not secure the diagnosis. The consent of the index case[27,28] should be obtained prior to offering cascade testing, and privacy legislation should be adhered to. Family dynamics sometimes limit the possibility of offering or performing cascade testing.

In Zehra's case, fasting lipid tests should be considered for both children, preferably by the age of 10 years.[1,4,6,10] It is worth counselling both parents about the 50% risk of each child having the condition and the advantages of early diagnosis.[5] It is also a good opportunity to re-enforce the need for an ongoing, low-fat family diet, regular exercise, avoiding obesity and smoking[1,4,6] and, if a child has FH, starting a low-dose statin from age 10 years to offer the best protection against the development of atherosclerosis.[1,6]

Zehra's husband should have fasting lipids checked plus review of his personal and family history of premature CVD, as well as physical examination to check for signs of FH. The chances of both parents having FH are small but need excluding, as the onset of premature CVD occurs in late childhood/early adolescence in children with homozygous FH.[5]

Zehra's brothers should also be tested, as they each have a 50% chance of having FH.

Answer 9

The outlook for FH is good provided patients are diagnosed early, maintain compliance with medications capable of reducing their LDL cholesterol levels to target, and maintain a healthy, low-fat diet, exercise regularly and avoid smoking. The major consequence of non-treated FH is premature CAD and death – in men this may be as high as 50% by age 50 years and up to 30% among women by age 60 years.[10] It can be difficult to convince children, teenagers and young people of the need for lifetime medications as they feel completely asymptomatic. Some patients who initially refuse treatment may change their mind if a significant event occurs in a friend or relative. An open door policy should be adopted to cater for such patients, and opportunistic targeting at routine clinic attendances may prove successful.

The current infrastructure in Australian primary care makes systematic cascade testing for GPs very challenging,[5,17,29] but improving patient, family and health professional awareness about FH coupled with support from the Heart Foundation and Primary Health Networks may effect change over time.

Answer 10

It is beneficial for FH to be managed together with the lipid specialist using shared-care follow-up. A Care Plan,[29] including team care arrangements with lipid specialist, dietician and exercise physiologist should be developed, with six-monthly reviews to monitor compliance and target goals. Cascade testing of close relatives is ongoing. With improved GP skills and confidence in FH detection and management combined with good patient engagement and compliance, low-complexity patients with FH can be managed in the primary care setting.

Resources for patients

- Heart Foundation; Familial hypercholesterolaemia, www.heartfoundation.org.au/images/uploads/publications/familial-hypercholesterolaemia.pdf

References

1. Nordestgaard B, Chapman M, Humphries S, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: Guidance for clinicians to prevent coronary heart disease: Consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34(45):3478–90a. doi: 10.1093/eurheartj/eht273.

2. Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. Int J Cardiol 2014;171(3):309–25. doi: 10.1016/j.ijcard.2013.11.025.
3. Brett T, Watts GF, Arnold-Reed DE, et al. Challenges in the care of familial hypercholesterolemia: A community care perspective. Expert Rev Cardiovasc Ther 2015;13(10):1091–100. doi: 10.1586/14779072.2015.1082907.
4. Wiegman A, Gidding SS, Watts GF, et al. Familial hypercholesterolaemia in children and adolescents: Gaining decades of life by optimizing detection and treatment. Eur Heart J 2015;36(36):2425–37. doi: 10.1093/eurheartj/ehv157.
5. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolaemia: A HuGE prevalence review. Am J Epidemiol 2004;160(5):407–20.
6. Watts GF, Sullivan DR, Poplawski N, et al. Familial hypercholesterolaemia: A model of care for Australasia. Atheroscler Suppl 2011;12(2):221–63. doi: 10.1016/j.atherosclerosissup.2011.06.001.
7. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients: Clinical guidance from the national lipid association expert panel on familial hypercholesterolemia. J Clin Lipidol 2011;5(3 Suppl):S1–8. doi: 10.1016/j.jacl.2011.04.003.
8. Nherera L, Calvert NW, DeMott K, et al. Cost-effectiveness analysis of the use of a high-intensity statin compared to a low-intensity statin in the management of patients with familial hypercholesterolaemia. Curr Med Res Opin 2010;26(3):529–36. doi: 10.1185/03007990903494934.
9. World Health Organization. Familial hypercholesterolaemia: Report of a second WHO consultation. Geneva: WHO, 1999.
10. Marks D, Thorogood M, Neil HA, et al. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis 2003;168(1):1–14.
11. Grundy SM, Stone NJ, Bailey AL, et al. 2018 Cholesterol Clinical Practice Guidelines. Circulation. 2018;000:e000–e000. doi: 10.1161/CIR.0000000000000625.
12. Expert Group for Cardiovascular. Introduction to lipid modification. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited, 2018.
13. NPS MedicineWise. Statin Medicines: Frequently asked questions. Surry Hills, NSW: NPS MedicineWise, 2017. Available at https://cdn0.scrvt.com/08ab3606b0b7a8ea53fd0b40b1c44f86/efdf0eb00342db0a/65e02d895101/Statins-FAQ.pdf [Accessed 17 December 2018].
14. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. Lancet 2010;375(9716):735–42. doi: 10.1016/S0140-6736(09)61965-6.
15. National Institute for Health and Clinical Excellence, The National Collaborating Centre for Primary Care. NICE Clinical Guideline 71: Identification and Management of Familial Hypercholesterolaemia. London, NICE: 2008 (Updated 2017). Available at www.nice.org.uk/guidance/cg71 [Accessed 24 November 2018].
16. Nordestgaard BG, Benn M. Genetic testing for familial hypercholesterolaemia is essential in individual cases with high LDL cholesterol: Who does it in the world? Eur Heart J 2017;38(20):1580–83. doi: 10.1093/eurheartj/ehx136.
17. Brett T, Qureshi N, Gidding S, Watts GF. Screening for familial hypercholesterolaemia in primary care: Time for general practice to play its part. Atherosclerosis 2018;277:399–406. doi: 10.1016/j.atherosclerosis.2018.08.019.
18. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. Circulation 2008;117(6):743–53. doi: 10.1161/CIRCULATIONAHA.107.699579.
19. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia: A scientific statement from the American Heart Association. Circulation 2015;132(22):2167–92. doi: 10.1161/CIR.0000000000000297.
20. Perez de Isla L, Alonso R, Mata M, et al. Predicting cardiovascular events in familial hypercholesterolaemia: The SAFEHEART Registry (Spanish Familial Hypercholesterolaemia Cohort Study). Circulation 2017;135(22):2133–44. doi: 10.1161/CIRCULATIONAHA.116.024541.
21. Brown MS, Goldstein JL. Familial hypercholesterolemia: Defective binding of lipoproteins to cultured fibroblasts associated with impaired regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity. Proc Natl Acad Sci U S A 1974;71(3):788–92.
22. Varret M, Abifadel M, Rabès JP, Boilaeu C. Genetic heterogeneity of autosomal dominant hypercholesterolemia. Clin Genet 2008;73(1):1–13.
23. Ademi Z, Watts GF, Pang J, et al. Cascade screening based on genetic testing is cost-effective: Evidence for the implementation of models of care for familial hypercholesterolaemia. J Clin Lipidol 2014;8(4):390–400. doi: 10.1016/j.jacl.2014.05.008.
24. Marks D, Wonderling D, Thorogood M, et al. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. BMJ 2002;324(7349):1303.
25. Hadfield SG, Horara S, Starr BJ, et al. Family tracing to identify patients with familial hypercholesterolaemia: The second audit of the department of health familial hypercholesterolaemia cascade testing project. Ann Clin Biochem 2009;46(Pt 1):24–32. doi: 10.1258/acb.2008.008094.
26. Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolaemia: JACC Scientific Expert Panel. J Am Coll Cardiol 2018;72(6):662–80. doi: 10.1016/j.jacc.2018.05.044.
27. Knowles JW, Rader DJ, Khoury MJ. Cascade screening for familial hypercholesterolemia and the use of genetic testing. JAMA 2017;318(4):381–82. doi: 10.1001/jama.2017.8543.
28. Morris JK, Wald DS, Wald NJ. The evaluation of cascade testing for familial hypercholesterolemia. Am J Med Genet A 2012;158A(1):78–84. doi: 10.1002/ajmg.a.34368.
29. Department of Health. Questions and answers on the Chronic Disease Management (CDM) items. Canberra, DOH: 2014. Available at www.health.gov.au/internet/main/publishing.nsf/Content/mbsprimarycare-chronicdiseasemanagement-qanda#what [Accessed 24 November 2018].

CASE

3 Arjun is changing

Arjun, aged 45 years, is a man with Down syndrome who lives in shared supported accommodation (SSA) near your surgery. You have not met him before. He attends the appointment with Steve, his key support worker (KSW). Steve has brought Arjun to see you as the staff have noticed some behaviours of concern. For the past few months, Arjun had been irritable and is now refusing to go to his day activity program.

Question 1

What are the underlying genetics of Down syndrome?

Question 2

What options are available to screen for Down syndrome prenatally?

Question 3

What background information do you need to know about Arjun before exploring Steve's current concern?

Further information

You determine that Arjun does not have a medical treatment decision maker (MTDM), so you suggest to Steve that the process of a Victorian Civil and Administrative Tribunal (VCAT) guardianship application be commenced. In the meantime, as any impending treatment can be considered routine, you feel comfortable continuing with Arjun's care.

Arjun speaks in short phrases (eg 'See Frozen movie') and has a mild dysarthria; there are times when those more familiar with his form of speech need to translate on his behalf. He can answer simple questions but struggles to answer some of your clinical questions.

Steve has worked in the house for seven years. As Arjun's KSW, he has an excellent relationship with Arjun and is encouraging and gentle to him during the consultation. There are a core group of five permanent staff who have been working at the house for over five years; other shifts are filled by casual or agency staff.

Arjun goes to Manor House Day Program five days a week, from 9.00 am to 3.00 pm. While there, he participates in community outings, like going to the local café or taking a bus trip to the National Gallery, and particularly enjoys music and dancing. He is capable of many independent activities of daily living (ADL), including personal hygiene and eating, but requires aids in more complex tasks like washing clothes or cooking.

Question 4

What causes of behavioural change will you consider, taking into consideration Arjun's intellectual disability?

Further information

You find out that Arjun was previously a lively, social person but has been very quiet since coming to the house. He spends long periods of his time in his room watching TV and looking at photographs. In the last few weeks, he has had sudden explosions of anger over minor requests by staff, such as asking him to come to dinner, or during interactions with other residents. Steve does not think Arjun has lost any skills, but says he is certainly refusing to do things he previously was happy doing, such as helping with the washing up and putting his clothes away.

Arjun's mother was diagnosed with advanced melanoma four years ago. As a result, she became increasingly unable to care for Arjun, ultimately resulting in Arjun's entering respite care for 18 months before living in the SSA for the

past six months. Arjun's mother died eight months ago. He has no local family members.

Steve reports that overnight staff have not heard or seen evidence of apnoeas or snoring. There have been no other environmental changes to either his home or day program that coincide with the onset of symptoms; in particular, there have been no changes to his sensory stimuli and no staff changes. There have been no changes to his medication and his last dental check, one month ago, was normal.

You conduct a thorough top-to-toe examination. As Arjun is not necessarily able to isolate where his issues are, you are very thorough when conducting your examination. You conduct a review of his cardiovascular and neurovascular system, finding no evidence of valvular heart disease or spinal cord impingement. You also look for signs of anaemia, thyroid disturbances, neck pain or physical abuse (eg, abnormal bruising patterns), but find nothing abnormal.

Question 5

What is the most likely diagnosis?

Question 6

What investigations should you order?

Further information

All of Arjun's tests come back normal. Using the DC-LD criteria, you diagnose him with depression, secondary to the death of his mother.

Question 7

How are you going to manage Arjun's depression?

Question 8

How would you address Arjun's grief?

Question 9

How should you monitor Arjun's progress?

CASE 3 Answers

Answer 1

Down syndrome is caused by a triplicate state, or trisomy, of all or a critical portion of chromosome 21. The majority (95%) of people with Down syndrome have three free copies of chromosome 21, and approximately 5% have a translocation. Approximately 95% of variants are on the maternally inherited allele, but it is not an inherited condition – it arises spontaneously from an error in cell division.[1]

Answer 2

There are three methods available to screen for Down syndrome prenatally.[2]

- The combined first-trimester screening (cFTS) is performed at between 11 and 14 weeks of gestation and uses three key points of information to determine an increased chance, but not a diagnosis, of Down syndrome: maternal age, fetal nuchal translucency (on ultrasound) and maternal serum markers for beta human chorionic gonadotropin and pregnancy-associated plasma protein A. It has an 85% sensitivity.
- The second trimester maternal serum screening is a quadruple test, factoring in maternal age and measuring alpha fetoprotein, human chorionic gonadotrophin, inhibin and unconjugated oestriol. It can be performed between 15 and 20 weeks of gestation. It has a 75% sensitivity.
- Non-invasive prenatal testing (NIPT) is performed from 10 weeks of gestation onwards. Trisomy 21 is detected by measuring cell-free DNA (cfDNA) fragments of chromosome 21 in the maternal serum, which can only be identified by comparing DNA in maternal and fetal plasma against a reference genome to determine point of origin. The improved sensitivity of cfDNA testing (>99%) offers more accurate assessment than other available screening methods.

As of July 2018, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists states that all options should be offered to the expectant mother. The main barrier will be cost, as the fee for NIPT can be upwards of $500, depending on the company used; in contrast, cFTS is supported by the Medicare Benefits Schedule. Out-of-pocket fees vary depending on the provider, from around $100 for the blood test plus the cost of ultrasonography.

The decision about whether to have the test and how the information obtained will be acted on (ie, continuing the pregnancy or termination) are separate and independent decisions. The woman and her partner should be supported and respected throughout the decision-making process.

Answer 3

You will need to know about Arjun's baseline characteristics to assess any recent changes – consider exploring his usual circumstances and behavioural patterns. Consider how best to communicate with Arjun to explore any current issues.

Communication

It should not be assumed that someone with Down syndrome cannot communicate for themselves. Even if there is a support person (family member or paid support worker) present, questions should be directed at the patient first. It is important to include the patient in the consultation, both verbally and nonverbally. Inclusion is courteous, and it builds rapport and encourages the patient to trust and cooperate with you throughout the consultation.[3]

The level of intellectual disability varies greatly among people with Down syndrome. Having a chat with Arjun about something of interest to him will give you a sense of his communication; both what he can understand (receptive abilities) and how he communicates (expressive skills). Arjun may use alternative communication devices or aids, and the person supporting him can help you understand and use these.

Support staff

You should know about the staff member's degree of involvement. As Arjun's KSW, Steve is likely to be well informed of his normal behaviour patterns and can judge the degree of change; alternatively, it may be a casual staff member accompanying him. Remember that disability support workers do not have health training, so avoid using medical jargon.

If the accompanying support worker does not know the person well and/or does not have the information you need, you can ring the house and talk to the House Supervisor, or request that the patient return for another appointment accompanied by someone who knows them well.

Capacity to consent

Determine Arjun's level of capacity to consent. In the event that he has been deemed incapable of making his own medical decisions, he may have an MTDM. Usually the MTDM is a family member who is involved in the person's life. In Victoria, under the *Medical Treatment Planning and Decisions Act 2016*, any individual may appoint an MTDM, whose role is to make 'a medical treatment decision on behalf of a person who does not have decision-making capacity'. The MTDM makes choices either to represent the individual on the basis of previously stated preferences or 'make a decision … that promotes the personal and social wellbeing of the person, having regard to the need to respect the person's individuality'. Steve is not Arjun's MTDM, and it is the general practitioner's (GP's) responsibility to determine who is.

However, if the GP is unable to locate the MTDM, in Victoria they can administer treatment 'if the medical treatment is routine treatment' or if 'the health practitioner believes that a further delay in carrying out the medical treatment would result in a significant deterioration of the person's condition'.[4] This law may vary in other states – consult with your medical indemnity insurer for more information.

In the event that there is no MTDM but one is required, an application may need to be submitted to VCAT (or relevant state/territory tribunal) to have a guardian appointed to make medical decisions.[5]

Living situation

When there is a rotating staff roster and multiple residents living in the one home, it is important to know the dynamics of the house. Find out about Arjun's day-to-day activities. People with a disability often attend a variety of day activities, which may include educational, recreational, social, volunteer and/or paid work. It is useful to know whether some aspect of the day activities has changed, as the change may have caused distress, which may present as behavioural change.

Baseline behaviour

For people with Down syndrome, changes in behaviour are a form of communication, and the underlying impetus can range from an expression of unmet wants and needs (eg for company, an activity); emotion (eg sadness, fear, loneliness, excitement); difficulty understanding (eg confusion, misunderstanding); physical pain/illness (eg dental, gastro-oesophageal reflux disease [GORD], infection, hypothyroidism); mental illness (eg anxiety, depression, mania, psychosis) or sensory deterioration (eg hearing, vision).[3]

Answer 4

Physical illness

Behaviour changes may be a reflection of a physical symptom that Arjun may not be able to articulate or identify. Ask about localised pain (eg musculoskeletal, or pain indicating the possibility of a urinary tract infection). Find out the date of Arjun's last dental review to rule out the possibility of dental pain. You should also review his medication to see whether there have been any additions or changes to dosage, as he may be experiencing side effects.

Consider conditions that are commonly associated with people with Down syndrome, like obstructive sleep apnoea, hypothyroidism and neck pain secondary to atlanto-axial instability[6] (presenting as neck pain or movement restriction [50%], weakness [70%] or pyramidal signs [90%] including hyperreflexia, loss of muscle tone in the lower extremities and decrease in fine motor coordination[7]). There are many medical conditions with a higher prevalence in adults with Down syndrome, including, but not limited to:

- endocrine: thyroid disease, diabetes
- gastrointestinal: GORD, coeliac disease
- mental health: depression, obsessive compulsive disorder, abuse
- eare, nose and throat: obstructive sleep apnea, hearing loss
- musculoskeletal: spinal cord compression, atlanto-axial instability, osteoporosis
- dental disease
- Alzheimer's dementia
- visual impairment, cataracts
- seizures (may be associated with Alzheimer's disease if >40 years of age)
- testicular cancer
- valvular heart disease.[8]

Table 1 lists conditions that have a higher prevalence in adults with Down syndrome.

Table 1. Characteristics of the study population according to age group

	Age <40 years; n=33 (55%)	Age ≥40 years, n=27 (45%)	*P* value
Demographic characteristics			
Age	29.5±6.4	46.0±4.6	<0.001
Female gender	19 (57.6%)	23 (85.2%)	0.020
Geriatric conditions			
Severe cognitive impairment	26 (78.8%)	13 (48.1%)	0.001
Behavioural symptoms	11 (33.3%)	14 (51.9%)	0.191
Functional impairment	8 (24.2%)	15 (55.6%)	0.017
Number of impaired ADL	0.5±1.1	1.5±1.5	0.005
Institutionalisation	0 (0.0%)	6 (22.2%)	0.006
Number of drugs used	2.0±1.2	3.0±1.4	0.016
Use of any psychotropic drugs	6 (18.2%)	17 (63.0%)	0.001
Nutritional problems			
Malnutrition (BMI <18.5kg/m^2)	1 (3.0%)	0 (0.0%)	1.000
Obesity (BMI ≥30.0kg/m^2)	4 (12.1%)	7 (25.9%)	0.197
Chronic diseases			
Epilepsy	1 (3.0%)	5 (18.5%)	0.081
Thyroid problems	24 (72.7%)	20 (74.1%)	1.000
Osteoporosis	7 (21.2%)	11 (40.7%)	0.156
Mood disorders	8 (24.2%)	11 (40.7%)	0.265
Cardiac problems	4 (12.1%)	6 (22.2%)	0.322

Values are reported as mean±standard deviation or frequency (%).
ADL, activities of daily living; BMI, body mass index

Reproduced from Carfi A, Antocicco M, Brandi V, et al. Characteristics of adults with Down syndrome: Prevalence of age-related conditions. Front Med (Lausanne) 2014;1:51.

Mental illness

The *Diagnostic criteria for psychiatric disorders for use in adults with learning disabilities* (2001) has similar criteria to depression in the *Diagnostic and statistical manual of mental disorders,* 5th edition, including that one of the key symptoms must either be depressed mood or anhedonia, that there are no other mental or physical conditions that would account for the symptoms and that the symptoms must be present for at least two weeks.[9] The symptoms must represent a change from the individual's premorbid state. In addition, the patient must have at least two more symptoms from a list of criteria that includes lethargy; tearfulness; loss of confidence, increased anxiety/fearfulness or increasing reassurance-seeking behaviour; sleep disturbance; weight change; reduced concentration; and an increase in retardation, somatic symptoms and motor retardation. For the complete criteria list, practitioners should consult the *Diagnostic criteria for psychiatric disorders for use in adults with learning disabilities* (2001).

Consider abuse: more than 25% of people who report sexual assault have a disability, and 90% of women with an intellectual disability have been sexually abused.[10]

Early-onset dementia (onset prior to 65 years) is very common in people with Down syndrome, affecting up to 55% of patients aged 40–59 years.[11] This is in contrast to the general population, for whom less than 1% of adults aged <65 years are affected.[12] It is important to remember this for Arjun, because the behavioural equivalents for depression and dementia may be similar. Look for changes in:

- memory – forgetting what day it is, or what he was going to do, or which staff are on, or names of familiar people (all in comparison to baseline)
- skills of daily function such as tending to personal care – washing, dressing, eating; doing domestic chores at home (laundry, dishes, cooking)
- communication
- orientation – getting lost in familiar places.

Sensory issues

New-onset disturbances to fundamental senses, like vision or hearing, can lead to behavioural changes. Cataracts are prevalent in 16.2% of people with Down syndrome aged 45–64 years, which is more than double the prevalence of the general population.[13] Regarding hearing, people with Down syndrome are prone to chronic ear infections and chronic middle ear effusions with associated hearing loss, airway obstruction and sleep apnoea, as well as problems with chronic rhinitis and sinusitis.[14] Up to 70% of people with Down syndrome have conductive and sensorineural hearing loss.[8] It is important to determine when Arjun's last hearing and vision check was.

Environmental changes

People with intellectual disability thrive in structure and routine. Life events, such as parental separations and death in families, have been identified as risk factors in depression for people with intellectual disability.[15] Review any staff changes at the SSA or Arjun's day placement.

If Arjun has presented like this before, determine the context of the previous situation, how it was resolved and if this new presentation is different. Look at the motivation behind the behaviours, and consider using a Durand Motivation Scale (www.ppboces.org/DocumentCenter/View/1937/Motivation_Assessment_Scale_II-12?bidId=).

The Durand Motivation Scale helps a clinician to determine the underlying motivation behind a behaviour. It distinguishes between sensory, escape, attention and tangible motivations, thereby aiding decision making as to what needs to be addressed.

History-taking is the most important part of determining a diagnosis. Remember to take a collateral history; for people with an intellectual disability, there are often many people who can observe their behaviour, including house staff, day program staff and family members.

Answer 5

Depression is the most likely diagnosis. The prevalence of depression in people with Down syndrome is upwards of 11%, and it is believed that people with Down syndrome are exposed to high levels of stressors that may increase the risk of the development of depression.[15] The other two key differentials are hypothyroidism and dementia, as both can present with lethargy and mood disturbances.

Answer 6

Consider conducting screening for causes that can present as dementia, which includes:[6,16]

- full blood count and other causes of anaemia, like vitamin B12, folate and iron
- erythrocyte sedimentation rate
- liver function test
- calcium
- thyroid function
- urine function test and other causes of acute delirium
- computed tomography (CT) scan of brain without contrast.

The blood tests would also rule out hypothyroidism as a differential diagnosis. You should consider a sleep study if there were a collateral history of witnessed snoring, witnessed apnoeas or daytime somnolence, or a CT cervical spine if there were signs of atlanto-axial instability.

Answer 7

The principles of managing depression in people with intellectual disability is the same as for the general population, but people with intellectual disability may experience barriers to care – for example, practitioners being reluctant to diagnose depression in someone who does not use speech to

communicate, or to treat depression with appropriate medical therapies, such as selective serotonin reuptake inhibitors (SSRIs) or electroconvulsive therapy.[6]

People with Down syndrome are at risk of being caught in a 'groove', a term to describe the emotional stagnation of depression that can be resistant to non-pharmacological treatment.[17] As such, SSRIs are considered first-line pharmacological treatment for depression, particularly because of the 'groove'. People with a developmental disability may have greater sensitivity to side effects, so commencement should begin at a low dose, and titration should be slower than in the general population.[6]

Psychotherapy may help some people with intellectual disability who are able to understand and use language. The more severe the cognitive and communication impairment, the more skills the practitioner requires. At present, there is no data to indicate whether there are any benefits to lifestyle measures such as physical activity or mindfulness-based exercises.

Engaging with Arjun's KSW as part of his management and support plan is important. Remember that Steve is not health trained, so providing psychoeducation to him means that there is someone monitoring Arjun's progress and reinforcing the coping strategies on a regular basis.[6] The KSW can also track an individual's response to SSRIs and report any side effects that occur. Mood and behaviour charts can be given to staff to quantifiably track a patient's progress.

Answer 8

Enabling people with intellectual disability to participate in the rites of passage and work through grief is often overlooked by both families and carers. The impact of the person's loss may be overlooked or dismissed as trivial, such as when a significant carer leaves, a housemate is relocated or there is a disruption of social networks at the day or recreational program.[6] There are many ways in which grief can be addressed for people with intellectual disability, including:

- using educational tools like social stories, or caring for plants or animals to discuss illness and death
- educating carers about how to address the patient's grief and allow them more time to process their feelings
- expressing feelings (eg art therapy, picture books)
- participating in rites of passage (eg arranging the funeral, visiting the grave)
- commemorating (eg creating a home memorial).

Answer 9

Arjun's medication should be reviewed no later than four weeks after initiation to review side effects and efficacy, then titrated appropriately. You should be clear about the length of the period of treatment to ensure that your patient is not left on the medication long term without just cause.

In future, Arjun should have an annual Comprehensive Health Assessment Program, a structured health assessment tool designed for people with intellectual disability to ensure they receive adequate health screening (www.oncall.com.au/wp-content/uploads/2018/06/CHAP_Version_15.pdf). This involves screening for the following issues.

For any man of a similar age:

- explore symptoms, lifestyle, modifiable risk factors, and psychosocial wellbeing; pay particular attention to smoking, nutrition, alcohol, and physical activity
- promote a low-calorie, high-fibre diet and regular exercise; monitor for obesity[18]
- assess blood pressure, body mass index and waist circumference; consider Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK)
- consider any personal or family history indications for additional screening (such as early cardiovascular disease or cancer).

For any person with Down syndrome of a similar age, conduct screening:

- six-monthly
  - dental health
- 12-monthly
  - thyroid dysfunction
  - dental disease
  - testicular check
  - medication review
  - urinary continence
  - mobility
  - annual influenza vaccination
- >12-monthly
  - bone density at age 40 years
  - hearing every 2–3 years
  - if using hearing aids, review as regularly as recommended by audiologist
  - vision every 2–3 years
  - if using glasses, review as regularly as recommended by optometrist.

Patients with Down syndrome should also be screened for the following conditions as required:

- dementia, keeping in mind that:
  - Mini–Mental State Examination is not validated for use in this population, but can be considered for those with mild intellectual disability
  - having a functional baseline from approximately 30 years of age is a useful comparison point; you can use a psychometric tool like the Vineland Adaptive Behaviour Scale, but it is likely easier to documentation of a person's

ADL, such as drawings, handwriting samples, photos of them participating in activities or videos

- symptoms of dementia in people with Down syndrome include:
  - repeated questioning
  - forgetting names
  - rummaging around looking for things
  - decline in language
  - declining in daily living skills
  - getting lost in familiar places
- it is necessary to distinguish from other causes of functional decline:
  - amotivation in depression is different from loss of skills
  - dyspraxia may present as change in function such as rolling clothes instead of folding them
  - visual or spatial skill loss may present as a change in artwork
- when making a diagnosis of dementia, it is important to show clear deterioration over a period of six months, which can be aided by documentation of baseline behaviour[6]

- valvular heart disease, particularly mitral valve prolapse and valvular regurgitation – careful auscultation should suffice and echocardiography considered if suspicion is high[7]
- epilepsy – people with Alzheimer's disease in conjunction with Down syndrome are also at a risk of developing epilepsy; data suggest that >80% of patients with Down syndrome and dementia will have concurrent epilepsy[17]
- vaccinations – ensure they have had the full course of pneumococcal vaccine
  - Down syndrome is considered a Category B condition of increased risk of invasive pneumococcal disease. It is recommended that people with Down syndrome have three lifetime doses – one dose of 23vPPV around 18 years of age, another five years later and another at least five years after that or at 65 years of age, whichever comes later.[19]

References

1. Online Mendelian Inheritance in Man, OMIM (TM). Johns Hopkins University, Baltimore, MD. MIM Number: 190685:2017. Available at www.omim.org/entry/190685 [Accessed 4 December 2018].
2. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions. East Melbourne, Vic: RANZCOG, 2018. Available at www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Prenatal-screening.pdf?ext=.pdf [Accessed 4 December 2018].
3. Tracy J. Australians with Down syndrome: Health matters. Aust Fam Physician 2011;40(4):202–08.
4. Victorian Legislation and Parliamentary Documents. Medical Treatment Planning and Decisions Act 2016. Melbourne: Victorian Government, 2016. Available at www.legislation.vic.gov.au/Domino/Web_Notes/LDMS/PubStatbook.nsf/f932b66241ecf1b7ca256e92000e23be/B4D3EBB66E52E98CCA25807A0014F70D/$FILE/16-069aa%20authorised.pdf [Accessed 2 December 2018].
5. Victorian Civil and Administrative Tribunal. Appoint a guardian or administrator for an adult with a disability. Melbourne: VCAT, [no date]. Available at www.vcat.vic.gov.au/get-started/guardianship-and-powers-of-attorney/appoint-a-guardian-or-administrator-for-an-adult [Accessed 11 January 2019].
6. Therapeutic Guidelines. Management guidelines: Developmental disability. Version 3. Melbourne: Therapeutic Guidelines Limited, 2012. Available at https://tgldcdp.tg.org.au/fulltext/quicklinks/management_guideline.pdf [Accessed 18 December 2018].
7. Yang SY, Boniello AJ, Poorman CE, Chang AL, Wang S, Passias PG. A review of the diagnosis and treatment of atlantoaxial dislocations. Global Spine J 2014;4(3):197–210.
8. Smith DS. Health care management of adults with Down syndrome. Am Fam Physician 2001;64(6):1031–38.
9. Smiley E, Cooper SA. Intellectual disabilities, depressive episode, diagnostic criteria and Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disabilities/Mental Retardation (DC-LD). J Intellect Disabil Res. 2003;47 Suppl 1:62–71.
10. Australian Human Rights Commission. Face the facts: Disability rights. Sydney: Australian Human Rights Commission, 2014. Available at www.humanrights.gov.au/sites/default/files/FTFDisability.pdf [Accessed 4 December 2018]
11. Shott SR. Down syndrome: Common otolaryngologic manifestations. Am J Med Genet C Semin Med Genet 2006;142(3):131–40.
12. Dementia Australia. Key Facts and Statistics. Barton, ACT: Dementia Australia: 2018. Available at www.dementia.org.au/media/key-facts-and-statistics [Accessed 9 November 2018]
13. Puri BK, Singh I. Prevalence of cataract in adult Down's syndrome patients aged 28 to 83 years. Clin Pract Epidemiol Ment Health 2007;3:26. doi:10.1186/1745-0179-3-26.
14. Hodapp R, Burke M, Finley C, Urbano R. Family caregiving of aging adults with Down syndrome. J Pol Pract Intellect Disabil 2016;13(2):181–89. doi: 10.1111/jppi.12153.
15. Walker JC, Dosen A, Buitelaar JK, Janzing JGE. Depression in Down syndrome: A review of the literature. Res Dev Disabil 2011;32(5):1432–40. doi: 10.1016/j.ridd.2011.02.010.
16. Pond D. Dementia: An update on management. Aust Fam Physician 2012;41(12):936–39.
17. McGuire DE, Chicoine B. Mental wellness in adults with Down syndrome: A guide to emotional and behavioral strengths and challenges. Bathesda, MD: Woodbine House, 2006.
18. Cohen W. Health care guidelines for individuals with Down syndrome – 1999 Revision. In: Down Syndrome. New York: John Wiley & Sons, 2003; p. 237–45.
19. Department of Health. Australian Immunisation Handbook: Pneumococcal disease. Canberra: DoH, 2018. Available at https://immunisationhandbook.health.gov.au/vaccine-preventable-diseases/pneumococcal-disease [Accessed 11 January 2019].

CASE

4 Rachel is concerned

Rachel, aged 32 years, consults you at six weeks' gestation in her first pregnancy. She is concerned about the possibility of having a child with a genetic disorder or disability and has read about genetic carrier screening prior to pregnancy.

Question 1

What information can you provide her about reproductive carrier screening?

Question 2

What other information should be sought from Rachel?

Further information

Rachel reports that her sister has a son, Oliver, who is two years of age and is not yet talking and who has been diagnosed with developmental delay. Oliver has been referred to a paediatrician for further assessment. There is no other significant family history reported.

Question 3

What concern is raised by this family history?

Question 4

What investigation would you recommend in Rachel's case?

Further information

Rachel elects to have a carrier test that includes testing for three disorders: Fragile X syndrome (FXS), spinal muscular atrophy (SMA) and cystic fibrosis (CF). As part of the consent process, Rachel is provided with information about the disorders to be screened, and it is explained to her that a normal result does not eliminate all risk of her having a child with one of the disorders. Rachel also agrees to contact her sister and ask for any further information about Oliver's condition and whether a genetic cause has been identified. After two weeks, Rachel's results are returned. The results are low risk of CF and SMA, but show that she is a carrier of a Fragile X premutation.

Question 5

What is FXS?

Question 6

What is the main implication of Rachel's Fragile X result?

Question 7

Are there any other health problems associated with Fragile X premutations?

Question 8

What further testing should be offered to Rachel?

Further information

Rachel's CVS reveals that the baby is a male who has inherited Rachel's normal copy of the Fragile X gene, and who will not have FXS.

Question 9

What alternative reproductive option is available to Rachel in future pregnancies?

Question 10

What information should be passed on to Rachel's family members?

CASE 4 Answers

Answer 1

Reproductive genetic carrier screening is a relatively new type of genetic test offered to women prior to pregnancy or in early pregnancy. Although carrier testing for CF has been available in Australia since 2006,[1] carrier screening has now expanded to encompass multiple genetic disorders. The American College of Obstetricians and Gynecologists has recommended that information about genetic carrier screening should be provided to all women who are pregnant or planning a pregnancy.[2] Options for carrier screening include screening with a panel for a limited selection of the most frequent conditions (eg CF, SMA and FXS)[3] or screening with an expanded panel that contains more than 100 disorders.[4] It is important to note that with all carrier screening there is a risk of false negative results, and therefore these tests do not eliminate all risk of having an affected child. Finally, in the absence of a family history, genetic carrier screening does not attract government funding in Australia, and so patients are required to pay the full cost of tests, which can range from $150 to more than $1000.

Answer 2

All couples who are pregnant or intending to have children should have a family history taken to identify relatives with heritable genetic disorders. Those identified with a family history of a specific inherited disorder should be offered referral to a genetic counselling service for information about carrier screening and reproductive options. For individuals of Eastern European (Ashkenazi) Jewish descent, additional screening should be offered for disorders that are more common in this population, such as Tay Sachs disease (a fatal genetic disorder of the central nervous system, with onset in infancy).[5] Individuals who trace their ancestry to countries in the Mediterranean, Asia, Middle East or Africa are at increased risk of being carriers of haemoglobinopathies such as thalassaemia, but haematological screening for haemoglobinopathies is recommended for all women regardless of ethnicity.

Answer 3

A maternal family history of developmental delay or intellectual disability in a male relative raises the possibility of an X-linked form of intellectual disability. There are many different forms of X-linked intellectual disability, but the most common and well recognised is FXS.[6,7] Approximately one in 300 Australian women are carriers of Fragile X.[8]

Answer 4

It is important that a specific diagnosis for developmental delay is sought in Oliver; however, given that Rachel is already pregnant, timely investigation in her is a priority. Rachel should be offered carrier testing for Fragile X, which could be performed in isolation or as part of a panel that includes carrier testing of other disorders.

Answer 5

FXS is the most common cause of inherited intellectual disability.[7] People with FXS can have developmental delay, learning difficulties and epilepsy, as well as some physical characteristics. These may include a long face, relatively large head, prominent ears, hypotonia and hypermobility.[9] Behavioural difficulties are common, and include autism, anxiety, hyperactivity, temper tantrums and poor impulse control. Poor eye contact and hand flapping are also common. Often the earliest manifestations of FXS are delays in motor milestones and speech, with walking and first words in boys with FXS occurring at mean age of 20 months. The features of FXS vary from mild to severe, but because FXS is located on the X chromosome, males are more likely to be severely affected than females. Intellectual disability is seen in approximately half of females with FXS.

There is no cure for FXS, although some educational, behavioural and medical interventions can improve outcomes for people with FXS,[7] and pharmacological management of behavioural issues may be beneficial.

Answer 6

The main implication of this result is that Rachel is at risk of having a child with intellectual disability due to FXS. The gene for Fragile X is called *FMR1* and is located on the X chromosome; therefore, inheritance follows an X-linked pattern (Figure 1). Near the start of the *FMR1* gene is a repeating section of three genetic letters, 'CGG'. The normal number of CGG repeats is <55, and >55 is regarded as an increased number. The number of CGG repeats can increase when the gene is passed from a parent to a child.[7]

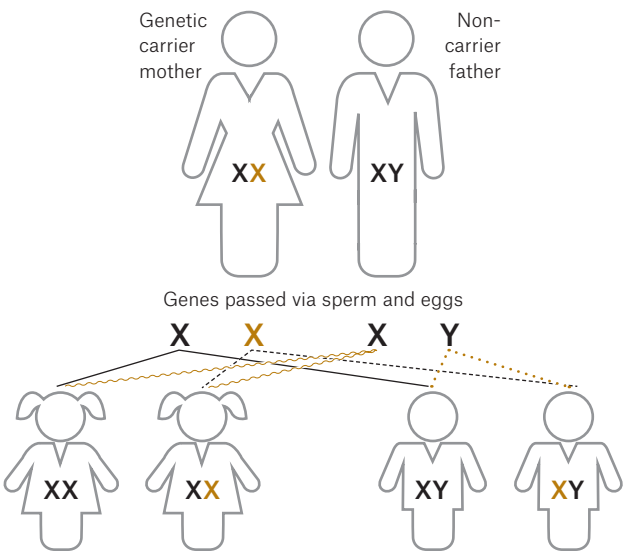

Figure 1. Inheritance following an X-linked pattern
FXS; Fragile X syndrome

When there are >200 CGG repeats, this is called a Fragile X 'full mutation' (Figure 2).[7] Males with a Fragile X full mutation almost always have intellectual disability that is usually of at least moderate degree. It is important to note that females with a Fragile X full mutation often have learning difficulties and sometimes have intellectual disability, but this is highly variable.

Between 55 and 200 CGG repeats is known as a Fragile X 'premutation' (Figure 2). When women who have a premutation have a child, there is a risk that the premutation will expand to >200 CGG repeats to become a full mutation.

Answer 7

Yes, women who have Fragile X premutations are at increased risk of premature ovarian insufficiency. Approximately one in five women who carry a premutation experience menopause prior to age 40 years,[7] and many experience milder forms of ovarian dysfunction such as irregular menses or reduced fertility.[9]

Premutation carriers are also at risk of a late onset neurological disorder called Fragile X–associated tremor/ataxia syndrome (FXTAS).[10] FXTAS is a neurodegenerative disorder associated with tremor, ataxia and memory problems. It primarily affects males with premutations but occasionally affects females. FXTAS does not affect individuals with full mutations, including those with FXS. There is also evidence that anxiety symptoms are more common in carriers of premutations than in the general population, and a selective serotonin reuptake inhibitor can be helpful for premutation carriers who have significant depression or anxiety.[11]

Answer 8

Rachel should be offered prenatal testing to determine whether or not the baby is affected by FXS. This is done by chorionic villus sampling (CVS), which can be performed after 11 weeks' gestation. CVS can determine whether the baby has inherited Rachel's normal X chromosome or the X chromosome with the expanded CGG repeat. If the baby has inherited the expanded CGG repeat, CVS will also show whether the CGG repeat has remained as a premutation (55–200 repeats) or expanded to a full mutation (>200 repeats), thus causing FXS. A diagnosis of full mutation by CVS would allow Rachel to choose to terminate the pregnancy or alternatively to prepare for the birth of a baby with FXS. Rachel should be informed that CVS is associated with an approximately 1 in 500 risk of procedure-related miscarriage.

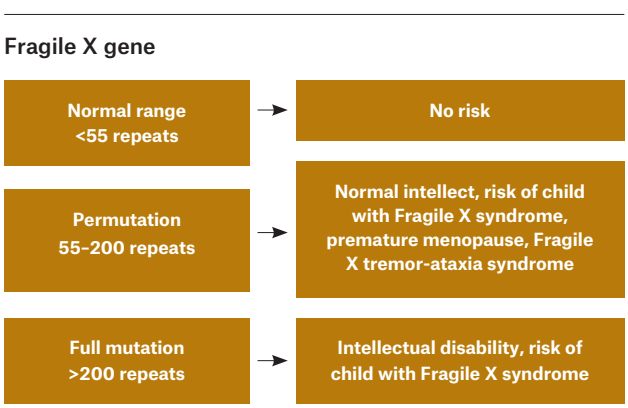

Figure 2. Relationship between number of repeats and degree of disability and risk

Answer 9

If increased genetic risk is identified prior to pregnancy, couples have the option of using in vitro fertilisation (IVF) and preimplantation genetic testing (PGT) as an alternative to prenatal diagnosis and potential termination of pregnancy. PGT involves using standard IVF procedures to create embryos that then undergo genetic testing on day five post-conception prior to transfer to the woman's uterus. Affected embryos are discarded, and the only unaffected embryos are transferred.

Answer 10

Rachel should be supported to pass on to her family information about the diagnosis of the Fragile X premutation. This is particularly relevant to Rachel's sister but may also be important for other family members. A referral to a clinical genetics service can facilitate cascade screening in the family and assist with the identification of at-risk relatives. Symptoms in relatives that should raise suspicion include premature menopause and late-onset tremor and ataxia.

References

1. Archibald AD, Massie J, Smith MJ, Dalton DG, du Sart D, Amor DJ. Population-based genetic carrier screening for cystic fibrosis in Victoria. Med J Aust 2014;200:205–06. doi: 10.5694/mja13.10864.
2. Committee on Genetics. Committee Opinion No. 691: Carrier screening for genetic conditions. Obstet Gynecol 2017;129(3):e41–e55. doi: 10.1097/AOG.0000000000001952.
3. Archibald AD, Smith MJ, Burgess T, et al. Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: Outcomes of 12,000 tests. Genet Med 2018;20:513–23. doi: 10.1038/gim.2017.134.
4. Kraft SA, Duenas D, Wilfond BS, Goddard KAB. The evolving landscape of expanded carrier screening: Challenges and opportunities. Genet Med 2018. doi: 10.1038/s41436-018-0273-4.
5. Lew RM, Burnett L, Proos AL, et al. Ashkenazi Jewish population screening for Tay-Sachs disease: The international and Australian experience. J Paediatr Child Health 2015;51(3):271–79. doi: 10.1111/jpc.12632.
6. Kraan CM, Godler DE, Amor DJ. Epigenetics of fragile X syndrome and fragile X-related disorders. Dev Med Child Neurol 2019;61(2):121–27.doi: 10.1111/dmcn.13985.
7. Saul RA, Tarleton JC. FMR1-related disorders. In Adam MP, Ardinger HH, Pagon RA, et al, editors. Seattle, WA: Gene Reviews, 1998 [updated 2012].
8. Kraan CM, Bui QM, Field M, et al. FMR1 allele distribution in 35,000 males and females: A comparison of developmental delay and general population cohorts. Genet Med 2018. doi: 10.1038/gim.2018.52.
9. Birch RC, Cohen JC, Trollor JN. Fragile X-associated disorders: Don't miss them. Aust Fam Physician 2017;46(7):487–91.
10. Hagerman RJ, Hagerman P. Fragile X-associated tremor/ataxia syndrome – Features, mechanisms and management. Nat Rev Neurol 2016;12(7):403–12. doi: 10.1038/nrneurol.2016.82.
11. Gossett A, Sansone S, Schneider A, et al. Psychiatric disorders among women with the fragile X premutation without children affected by fragile X syndrome. Am J Med Genet B Neuropsychiatr Genet 2016;171:1139–47.

CASE

5 Nancy wonders if she has Huntington's disease

Nancy, a schoolteacher aged 42 years, presents to your clinic nine months after her father died from Huntington's disease (HD) aged 64 years. Since then, she has found it difficult to concentrate at work, and has been waking up at 4 am and unable to get back to sleep. Nancy has been well otherwise. She is a non-smoker, drinks 2–3 glasses of wine per day, and does not take any regular medications.

Question 1

What do you know about HD and its genetics?

Question 2

What is your approach to Nancy's presentation?

Question 3

What do you believe to be the most likely cause of Nancy's symptoms?

Further information

Nancy returns to your clinic six months later, feeling and sleeping well, and is back to her normal level of function at work. She knows that HD is an autosomal dominant disorder, which means she, as an individual, has a one in two, or 50:50, chance of inheriting the illness from her father. She asks you whether you think she has HD.

Question 4

What symptoms will you ask about, and what will you consider in your physical examination to assess for clinical features of Huntington's disease?

Further information

Nancy does not report any symptoms suggestive of clinical HD, and there is no chorea on examination. You confirm this with collateral history from her son, who reports that although her mood is low she is otherwise her 'usual self'. You explain your findings and she is reassured. She also understands that just because she currently does not have clinical manifestations of HD, it does not necessarily mean that she does not carry the abnormal CAG expansion.

Two years later, Nancy, who has informed her adult son about HD, comes back to the clinic, asking whether she could have a genetic test. This has been prompted by her son and daughter-in-law's plan to start a family.

Question 5

How will you approach your discussion with Nancy about genetic testing for HD?

Further information

Nancy decides to proceed with genetic testing. She chooses to do this because she would like her children to know if they are at risk of passing on the gene, prior to having children.

You receive a letter from the clinical geneticist. Nancy was found to have 42/18 CAG repeats. Since one of Nancy's two copies of the *Huntingtin* gene had >35 CAG repeats, and HD is an autosomal dominant disorder, Nancy is highly likely to develop clinical manifestations of HD within her lifetime.

Question 6

What would you recommend to Nancy, given the genetic test result?

Further information

Six years after your initial consultation, Nancy presents to your clinic, noting gradual deterioration in her work performance over the preceding six months. In particular, she is finding it increasingly difficult to help multiple students if they require her attention at the same time.

Question 7

How will you proceed with Nancy's management now?

CASE 5 Answers

Answer 1

HD is an autosomal dominant, progressive, neurodegenerative disorder, due to abnormal cytosine-adenosine-guanine (CAG) expansion in the chromosome 4 *huntingtin* gene. Being autosomal dominant, each offspring of someone with HD will have a one in two, or 50:50, chance of inheriting the abnormal CAG expansion. This probability applies to each offspring, regardless of the status of their siblings. Typical age of onset is 30–50 years, although age of onset can range from childhood to the 90s. Clinical manifestations of HD include involuntary movements, cognitive impairment, behavioural changes and psychiatric symptoms. While symptomatic treatments exist, there are no disease-modifying treatments at present.

Answer 2

Your history-taking confirms that Nancy has low mood and has been teary. She feels sad about her father's death and hopeless about her future, with the possibility of having HD herself. She is no longer enjoying things that used to give her pleasure and worries that she is a burden to her son. She has flat affect but does not have any suicidal thoughts.

Answer 3

It has been nine months since Nancy's bereavement. Since that event, she has been experiencing symptoms consistent with depression. On that basis you suspect a diagnosis of

adjustment disorder with depressed mood. You suspect her low mood could explain her cognitive symptoms. You refer Nancy to a psychologist for counselling, and also start her on a low dose of selective serotonin reuptake inhibitor.

Answer 4

HD can affect a person's motor function, cognition and mental health.

Chorea (a brief, jerky, involuntary movement) is one of the key motor manifestations of HD.[1] A video of someone with HD and chorea can be found in the case report by Malekpour and Esfandbod (2010).[1] Because of the nature of the movement, early and mild forms of chorea can be mistaken for restlessness or clumsiness. The onset of clinical HD has previously been defined by the onset of chorea; however, longitudinal studies of HD genetic expansion carriers suggest that cognitive impairment often precedes chorea.[2] Other motor manifestations of HD include unsteadiness, falls and dysphagia, all of which may benefit from allied health input.

HD affects the frontostriatal circuit in the brain and can lead to cognitive and behavioural changes. People with HD may report difficulty with multitasking, memory recall and planning/execution of complex tasks. People with HD can also develop behavioural symptoms and become irritable, with little insight at times. It is essential to obtain corroborative history independently, from family and friends.

Finally, while psychosis is rare, depression is very common in HD, and the risk of suicide is up to eight times that of the general population.[3] This is a very important, and potentially treatable, cause of mortality that health practitioners should be vigilant about.

Answer 5

In Australia, genetic testing in a pre-symptomatic person (ie, someone with no clinical manifestations of HD) is carried out by a clinical geneticist, while confirmatory genetic testing for someone with clinical manifestations can be carried out by other suitably qualified doctors such as neurologists and psychiatrists with an interest in HD.

You repeat the history-taking. There are no symptoms suggestive of clinical HD and you cannot see any involuntary movements either. Importantly, Nancy is not depressed and has no suicidality.

Satisfied that Nancy is 'pre-symptomatic', you arrange a consultation at the local genetic counselling service. Part of the counselling will explore issues including:

- the genetics and inheritance of HD
- that the genetic test result cannot predict the age of onset, severity or progression of disease
- there is currently no proven therapy to slow HD or delay onset, so there are both potential harms and benefits of knowing one's genetic status; this is a very personal decision and varies across individuals
- implications for insurance and other family members.

You explain to Nancy that this will involve two counselling sessions, and that she can change her mind any time if she decides that she no longer wants to receive her genetic test results. The process can take some time, as an international protocol for pre-symptomatic genetic testing specifies a waiting period between the request and performance of a genetic test. For further information, you give Nancy a weblink for a booklet about genetic testing in HD, published by the Centre for Genetics Education.[4]

Answer 6

Currently, there is no proven intervention that would prevent or slow down the onset of clinical HD among expansion carriers. Nonetheless, there is observational data to suggest that excessive alcohol[5] and a passive lifestyle[6] may be associated with earlier disease onset. On this basis, you advise Nancy to reduce her alcohol intake and adopt an active lifestyle. You also advise Nancy to discuss her test result with her siblings and adult children. In particular, you recommend her son to see a genetic counsellor, as there are now options, such as in vitro fertilisation and pre-implantation genetic testing, which would allow her son to have children who do not have HD. There are HD patient associations in every state in Australia and many people have found the support groups helpful.

Answer 7

You repeat the history-taking for HD manifestations. Nancy has noted unsteadiness in her walking and also increasing forgetfulness over the past six months. You note some involuntary movements in Nancy's feet and trunk, which Nancy is not aware of. Nancy is not depressed or suicidal. There is a multidisciplinary HD service in your state, and you refer Nancy to the service for further assessment and management.

Conclusion

The HD neurologist agrees that Nancy has clinical manifestations of HD, with mild motor impairment (including mild chorea in trunk and limbs) and mild cognitive deficits. There is a medication (tetrabenazine) that has been approved specifically for suppressing chorea in HD.[7] However, the movements do not concern Nancy, and they have not caused any injury. Suppression of chorea does not change the long-term outlook for HD, whereas tetrabenazine can be associated with side effects including depression and dysphagia.[7] Following discussion with Nancy and her family, it is decided that Nancy does not need tetrabenazine at this stage. The neurologist explains that there is much research underway for HD, including clinical trials using gene-silencing anti-sense oligonucleotides,[8] and there is much hope for HD.

Nancy also undergoes physiotherapy, speech pathology and dietetic reviews. She is at an early stage of HD and is therefore assigned a social worker as her key worker. She continues to attend your clinic with a shared-care arrangement. Nancy finds involvement in her local HD patient association very helpful. You also find the education program designed by the Huntington Study Group, including online CME videos, helpful for Nancy's ongoing care.[9]

Clinician resources

- The Huntington Study Group has designed a free online education program, including CME videos, https://huntingtonstudygroup.org/education

Patient resources

- The Huntington's NSW and ACT website contains many helpful links to information on HD, www.huntingtonsnsw.org.au
- HDBuzz is a helpful news site on HD research, written by scientists in plain language, https://en.hdbuzz.net

References

1. Malekpour M, Esfandbod M. Images in clinical medicine. Huntington's chorea. N Engl J Med 2010;363(15):e24. doi: 10.1056/NEJMicm0908798.
2. Loy CT, McCusker EA. Is a motor criterion essential for the diagnosis of clinical Huntington disease? Version 2. PLoS Curr. 2013;5. doi: 10.1371/currents.hd.f4c66bd51e8db11f55e1701af937a419.
3. Schoenfeld M, Myers RH, Cupples LA, Berkman B, Sax DS, Clark E. Increased rate of suicide among patients with Huntington's disease. J Neurol Neurosurg Psychiatry 1984;47(12):1283–87.
4. Centre for Genetics Education. Huntington disease and genetic testing. St Leonards, NSW: Centre for Genetics Education, 2017. Available at www.genetics.edu.au/publications-and-resources/booklets-and-pamphlets/huntington-disease-and-genetic-testing [Accessed 17 January 2019].
5. Schultz JL, Kamholz JA, Moser DJ, Feely SM, Paulsen JS, Nopoulos PC. Substance abuse may hasten motor onset of Huntington disease: Evaluating the Enroll-HD database. Neurology 2017;88(9):909–15.
6. Trembath MK, Horton ZA, Tippett L, et al. A retrospective study of the impact of lifestyle on age at onset of Huntington disease. Mov Disord 2010;25(10):1444–50.
7. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: A randomized controlled trial. Neurology 2006;66(3):366–72.
8. Carroll J. Advances on many fronts in the battle against the protein that causes Huntington's disease. HDBuzz. 4 December 2018. Available at https://en.hdbuzz.net/266 [Accessed 17 January 2019].
9. Huntington Study Group. HD education. Rochester, NY: Huntington Study Group, [date unknown]. Available at https://huntingtonstudygroup.org/education [Accessed 17 January 2019].

ACTIVITY ID **150242**

Genetics

This unit of *check* is approved for six Category 2 points in the RACGP QI&CPD program. The expected time to complete this activity is three hours and consists of:

- reading and completing the questions for each case study
  - you can do this on hard copy or by logging on to the *gplearning* website, http://gplearning.racgp.org.au
- answering the following multiple choice questions (MCQs) by logging on to the *gplearning* website, http://gplearning.racgp.org.au
  - you must score ≥80% before you can mark the activity as 'Complete'
- completing the online evaluation form.

You can only qualify for QI&CPD points by completing the MCQs online; we cannot process hard copy answers.

If you have any technical issues accessing this activity online, please contact the *gplearning* helpdesk on 1800 284 789.

If you are not an RACGP member and would like to access the *check* program, please contact the *gplearning* helpdesk on 1800 284 789 to purchase access to the program.

Case 1 – Jessica

Ashley brings her daughter, Jessica, aged three years, to see you. Jessica has been troubled by a persistent cough that has not settled despite a variety of cough syrups from the pharmacy.

Question 1

By defintion, a child with a chronic cough has daily coughing for more than:

A. four weeks

B. six weeks

C. eight weeks

D. 12 weeks.

Further information

You take a detailed history and perform a careful physical examination. Neither reveal any specific clues as to the cause of her cough. You decide the next step is an investigation.

Question 2

Which one of the following is the most appropriate investigation for a child three years of age with a non-specific chronic cough?

A. Spirometry

B. Chest X-ray

C. Blood gas analysis

D. Nasopharyngeal swab polymerase chain reaction (PCR)

Case 2 – Xing

Xing, aged 28 years, has recently arrived in your suburb from interstate. At this stage you do not have access to his previous medical records, but he states that there was nothing of concern other than a diet adjustment for an elevated cholesterol level. He presents today for a check-up.

Question 3

Which one of the following levels of low-density lipoprotein (LDL) cholesterol in mmol/L would be highly suspicious of familial hypercholesterolaemia (FH)?

A. 4.5

B. 5.5

C. 6.5

D. 8.5

Further information

Further investigation confirms that Xing has FH. Xing is now very concerned that his siblings may also have FH and be unaware.

Question 4

Which one of the following best describes the risk his brother has of FH?

A. 10%

B. 25%

C. 50%

D. 100%

Case 3 – Antoinette

Your next patient is Antoinette, an accountant aged 28 years who has been coming to this practice for many years. Antoinette is excited to tell you that her home pregnancy test was positive, and she is seeking to share her antenatal care with you and the local public hospital.

Antoinette is worried about trisomy 21, as her work colleague had a positive result when screened for trisomy 21 on antenatal screening. Antoinette is keen to discuss prenatal testing for this condition.

Question 5

Which one of the following antenatal screening tests has the highest sensitivity?

A. Combined first-trimester screening (cFTS)

B. Second trimester maternal serum screening (quadruple test)

C. Non-invasive prenatal testing (NIPT)

D. Fetal nuchal translucency (on ultrasound)

Further information

Antoinette is keen to undertake the NIPT test and asks for more information about how this works.

Question 6

NIPT measures:

A. pregnancy-associated plasma protein A (PAPP-A) in the amniotic fluid

B. PAPP-A in the maternal serum

C. cell-free DNA (cfDNA) fragments of chromosome 21 in the amniotic fluid

D. cfDNA fragments of chromosome 21 in the maternal serum.

Further information

Antoinette has also read about other new screening tests for inherited intellectual disabilities.

Question 7

Which one of the following is the most common cause of inherited intellectual disability?

A. Tay Sachs disease

B. Fragile X syndrome (FXS)

C. Spinal muscular atrophy

D. Cystic fibrosis

Further information

Antoinette thinks there may be a family history of intellectual disability and wonders how that affects her risk.

Question 8

Which one for the following features in the family history raises the possibility of an X-linked form of intellectual disability?

A. Maternal family history of intellectual disability in a male relative

B. Maternal family history of intellectual disability in a female relative

C. Paternal family history of intellectual disability in a male relative

D. Paternal family history of intellectual disability in a female relative

Case 4 – Dorothy

Erica comes to see you to discuss her older sister Dorothy, aged 64 years. It appears that Dorothy has slowly worsening cognitive function despite her relatively young age. Erica is very worried that her sister might have Huntington's disease (HD), as there are whispers in her family history that one of her ancestors in the 19th century had this disease.

You ask Erica to describe Dorothy's health.

Question 9

Which one of the following is **not** a common motor manifestation of HD?

A. Chorea

B. Falls

C. Dysphagia

D. Tremors

Further information

Erica is even more concerned and asks about preventative strategies, assuming tests confirm HD in her sister.

Question 10

Which intervention has been proven to slow the onset and progression of HD in carriers?

A. Selective serotonin reuptake inhibitor antidepressants

B. Benzodiazepines

C. Tetrahydrocannabinol oil

D. None of the above

check

Independent learning program for GPs