Seminar

Down's syndrome

Nancy J Roizen, David Patterson

The sequencing of chromosome 21 and the use of models of Down's syndrome in mice have allowed us to relate genes and sets of genes to the neuropathogenesis of this syndrome, and to better understand its phenotype. Research in prenatal screening and diagnosis aims to find methods to identify fetuses with Down's syndrome, and reduce or eliminate the need for amniocentesis. Other areas of active research and clinical interest include the association of Down's syndrome with coeliac disease and Alzheimer's disease, and improved median age of death. Medical management of the syndrome requires an organised approach of assessment, monitoring, prevention, and vigilance. Improvements in quality of life of individuals with Down's syndrome have resulted from improvements in medical care, identification and treatment of psychiatric disorders (such as depression, disruptive behaviour disorders, and autism), and early educational interventions with support in typical educational settings. Approaches and outcomes differ throughout the world.

Genetics of chromosome 21 and Down's syndrome

In 1959 Lejeune, Gautier, and Turpin discovered the association between Down's syndrome and a third chromosome 21.[1] The recent sequencing of chromosome 21, in principle, allows the identification of every gene on the chromosome.[2] In the original manuscript, in which the sequencing and annotation for gene content was described, 225 genes or predicted genes were identified. The gene content of chromosome 21 is now estimated to be 329, including 165 experimentally confirmed genes, 150 gene models based on expressed sequence tag databases, and 14 computer predictions (see http://www-eri.uchsc.edu). An additional, unexpected finding is that the actual fraction of chromosome 21 that is transcribed into RNA might be an order of magnitude higher than the fraction occupied by gene coding sequences.[3]

One striking conclusion that can be drawn from the gene content of chromosome 21 is that there are sets of genes on the chromosome that are involved in the same metabolic pathway or biological system. For example, there are at least 16 genes or predicted genes that seem to participate in mitochondrial energy generation and reactive oxygen species metabolism (panel 1).[2] Several studies have linked mitochondrial dysfunction with Down's syndrome and Alzheimer's disease.[4,5] Capone[6] discussed ten genes that exert an influence on central nervous system structure or function, and might have a role in the neuropathogenesis of Down's syndrome (panel 2). Schupf and Sergievsky[7] reported that both host factors and *APP* gene overexpression might account for variation in age of onset of dementia in Down's syndrome.

We still know little about the causes of non-disjunction that lead to Down's syndrome. Findings that showed an association of some polymorphisms in genes encoding enzymes of folate metabolism[8] were confirmed by one follow-up study,[9] but were not replicated by another.[10] Folate is necessary for methyl group metabolism, including methylation of DNA, and hence control of gene expression. At least six genes on chromosome 21 might have a role in folate or methyl group metabolism (panel 3).[2,11–15] An observation by Doolin and colleagues[16] could help to explain some inconsistencies in this area; these investigators showed that two different mechanisms might contribute to the effects of polymorphisms in genes involved in folate metabolism. Apparently, both the genotype of the mother and the genotype of the embryo should be considered in assessment of the role of gene polymorphisms in this pathway.

The use of models of Down's syndrome in mice is one of the most promising approaches to understanding the phenotype. The genes found on human chromosome 21 are found on three separate mouse chromosomes.[17] While trisomy of the entire mouse chromosome is usually lethal, Reeves and colleagues[18] reported production of a segmental trisomy of part of mouse chromosome 16. Mice with this trisomy show many of the features seen in people with Down's syndrome, such as deficits in learning,[19] craniofacial maldevelopment,[20] and neuropathological changes associated with Alzheimer's disease.[21]

Pregnancy screening, prenatal diagnosis, and epidemiology

The diagnosis of Down's syndrome is made by chromosome analysis, which can be initiated prenatally due to identified risk factors, or postnatally due to the characteristic appearance of the infant (panel 4).[22] Prenatal diagnosis for chromosomal anomalies was first introduced in the 1970s, and was initially restricted to amniocentesis in the second trimester. At present, the standard of care in the USA is to offer pregnancy screening for chromosomal anomalies and spina bifida by a blood test to all women, followed by prenatal cytogenic diagnosis

Search strategy and selection criteria

Data for this seminar were identified by searches of Medline with the search term Down syndrome and individual topics. We focused on publications in the past 5 years and included highly regarded older publications. We followed the Health Supervision for Children with Down Syndrome guidelines developed by the American Academy of Pediatrics Committee on Genetics[17] and the guidelines of the Down Syndrome Medical Interest Group[18] and discussed the areas of controversy.

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SUNY Upstate Medical University, Syracuse, NY, USA (Prof N J Roizen MD)**; and Eleanor Roosevelt Institute Denver, CO, USA** (Prof D Patterson PhD)

Correspondence to: Prof Nancy J Roizen, Department of Pediatrics, SUNY Upstate Medical University, 750 East Adams Street Syracuse, NY 13210, USA
(e-mail: roizenn@upstate.edu)

Panel 1: **16 genes on chromosome 21 with a role in energy and reactive oxygen species metabolism**

Symbol	Name
BTG3	BTG family, member 3
MRPL39	Mitochondrial ribosomal protein L39
ATP5J	Mitochondrial coupling factor 6
GABPA	GA binding protein transcription factor, alpha subunit 60kDa
BACH1	BTB and CNC homology 1, basic leucine zipper transcription factor 1
SOD1	Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))
CRYZL1	Crystallin, zeta (quinone reductase)-like
ATP5O	ATP synthase H+ transporting, mitochondrial F1 complex, O subunit (oligomycin sensitivity conferring protein)
MRPS6	Mitochondrial ribosomal protein S6
DSCR1	Down syndrome critical region 1
CBR1	Carbonyl reductase 1
CBR3	Carbonyl reductase 3
SH3BGR	SH3 domain binding glutamic acid-rich protein
NDUFV3	NADH dehydrogenase (ubiquinone) flavoprotein 3, 10kDa
SNF1LK	SNF1-like kinase
C21orf2	Chromosome 2 open reading frame (mitochondrial protein)

Genes are listed in order from the centromere to the telomere on chromosome 21. There might be additional genes in the group that have not yet been identified.

if indicated. The combined serum test (measurement of alphafetoprotein, human chorionic gonadotropin, and unconjugated oestriol in maternal serum) in the first trimester has a 69% detection rate and a 5% false-positive rate.[23] Research efforts now focus on improvement of the sensitivity and specificity of screening, to reduce or eliminate the number of women needing an invasive diagnostic test, such as chorionic-villus sampling or amniocentesis.[24] The combined use of maternal serum screening with fetal ultrasound testing for a thickened nuchal fold may have an 80–85% detection rate with a 5% rate of false-positives.[25] Use of fetal cells in the maternal circulation for prenatal diagnosis[26] could eliminate the need for amniocentesis in diagnostic testing; however, isolation of fetal cells from maternal blood is still associated with several technical and biological difficulties. In some centres for in-vitro fertilisation, preimplantation screening is available as a prevention option.[27]

Calculation of the frequency of Down's syndrome depends on whether maternal age, gestational timing of diagnosis, and case loss due to prenatal diagnosis and termination of pregnancy are taken into account.[28,29] In a report from France, of 280 fetuses with Down's syndrome, 27% of the pregnancies were terminated, 4% were late spontaneous abortions or stillbirths, and 12% died in the first year of life; additionally, 12% were available for adoption. Of the 33 (12%) babies who died in their first year, 22 had medical problems, two died of sudden infant death syndrome, there was one infanticide, and eight deaths were unexplained.[30] Reports from various countries show several trends over the past two decades. The number of Down's syndrome fetuses conceived has increased as the mean age of pregnant women has increased. The number of terminated pregnancies with Down's syndrome has increased, and the prevalence of Down's syndrome births has decreased from one in 700 to about one in 1000.[31–35]

Assessment and management

The American Academy of Pediatrics[36] and the Down's Syndrome Medical Interest Group[37] have developed guidelines for the medical management of individuals with Down's syndrome. Reviews that focus on the medical problems of adolescents[38] and adults[39] have also been developed. Assessment, monitoring, prevention, and vigil-

Panel 2: **Genes localised to chromosome 21 that possibly affect brain development, neuronal loss, and Alzheimer's type neuropathology**

Symbol	Name	Possible effect in Down's syndrome
SIM2	Single-minded homolog 2 (Drosophila)	Brain development: required for synchronised cell division and establishment of proper cell lineage
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	Brain development: expressed during neuroblast proliferation and believed important homologue in regulation of cell-cycle kinetics during cell division
GART	Phosphoribosylglycinamide formyltransferase Phosphoribosylglycinamide synthetase Phosphoribosylaminoimidazole synthetase	Brain development: expressed during prenatal development of the cerebellum
PCP4	Purkinje cell protein 4	Brain development: function unknown but found exclusively in the brain and most abundantly in the cerebellum
DSCAM	Down syndrome cell adhesion molecule	Brain development and possible candidate gene for congenital heart disease: expressed in all molecule regions of the brain and believed to have a role in axonal outgrowth during development of the nervous system
GRIK1	Glutamate receptor, ionotropic, kainite 1	Neuronal loss: function unknown, found in the cortex in fetal and early postnatal life and in adult primates, most concentrated in pyramidal cells in the cortex
APP	Amyloid beta (A4) precursor protein (protease nexin-II, Alzheimer disease)	Alzheimer's type neuropathy: seems to be involved in plasticity, neurite outgrowth, and neuroprotection
S100B	S100 calcium binding protein, beta (neural)	Alzheimer's type neuropathy: stimulates glial proliferation
SOD1	Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis, adult)	Accelerated ageing? Scavenges free superoxide molecules in the cell and might accelerate ageing by producing hydrogen peroxide and oxygen

Panel 3: **Six genes with a role in folate and methyl group metabolism**

Symbol	Name
N6AMT1	Putative N6 DNA methyltransferase
CBS	Cystathionine-beta-synthase
DNMT3L	DNA (cytosine-5-)-methyltransferase-like
SLC19A1	Solute carrier family 19 (folate transporter), member 1
FTCD	Formiminotransferase cyclodeaminase
HRMT1L1	HMT1 hnRNP methyltransferase-like 1 (*S cerevisiae*)

Genes are listed in order from the centromere to the telomere on chromosome 21. There might be additional genes in the group that have not yet been identified.

ance play a part in management of children, adolescents, and adults with Down's syndrome (panel 5).[36,37]

Assessment of newborns

Soon after birth, all children with Down's syndrome should be assessed for congenital heart disease, hearing loss, and ophthalmological problems. About half of children with Down's syndrome are born with congenital heart disease.[40] The most frequent lesions are atrioventricular septal defect (45% of newborns with Down's syndrome) and ventricular septal defect (35%); isolated secundum atrial septal defects (8%), isolated persistent patent ductus arteriosus (7%), isolated tetralogy of Fallot (4%), and other lesions (1%) can also arise. Assessment of all newborns with Down's syndrome with an echocardiogram is the standard recommendation.[36,37] Symptoms of serious heart disease may be absent or hidden due to the tendency of children with Down's syndrome to develop pulmonary vascular resistance. Adolescents and young adults with no known intracardiac disease can develop mitral valve prolapse (46%) and aortic regurgitation (17%).[41] Most experts recommend assessment of adult patients who have symptoms or signs of valvular disease on clinical examination,[37] but some advocate a second cardiac assessment for all young adults.[42]

Identification and treatment of hearing loss is an important part of medical management in individuals with Down's syndrome. Between 38% and 78% of people with Down's syndrome have this problem,[43–45] which can be conductive, sensorineural, or mixed. Medical management for conductive hearing loss frequently includes medical treatment of otitis media and serous otitis media. Surgical interventions with combinations of pneumoeustachian tubes, tonsillectomy, and adenoidectomy are common. Speech therapy, communication with signing and assisted communication methods, hearing aids, and cochlear implants are also used.

Panel 4: **Phenotypic features of Down's syndrome**

Brachycephaly
Brachydactyly
Broad hands
Duodenal atresia
Epicanthal folds
Fifth finger clinodactyly
Flat nasal bridge
Hypotonia
Lax ligaments
Mental retardation
Open mouth
Short stature
Wide 1–2 toe gap

Findings of two studies question the effectiveness of pneumoeustachian tubes in children with Down's syndrome: in a study with Down's syndrome children, aged 6–15 years, who had not previously had pneumoeustachian tubes, 40% continued to have hearing loss after placement.[46] Iino[47] studied 28 children with pneumoeustachian tubes placed after 2 years of age. Compared with controls, the children with Down's syndrome had a lower cure rate, more sequelae (atelectatic eardrum, permanent perforation of the eardrum, and middle ear cholesteatoma), more frequent episodes of otorrhea and antibiotic-resistant bacterial infection, and lower rates of improvement in hearing acuity after tube placement. The findings of the first 18 months of a longitudinal study[48] of medical and surgical treatment for the otolaryngologic features of Down's syndrome give hope for maintenance of normal hearing. 48 children entered the study at less than 24 months of age and, at least every 6 months, underwent a full ear, nose, and throat examination and an audiogram. During the next 18 months, only eight children were free or nearly free from ear infections. 40 children had tubes placed: 45% once, 43% twice, 7·5% three times, and 5% four times. When the tubes were removed, fluid reaccumulated. When four children had a normal audiogram without antibiotics or tubes, but only one had abnormal hearing.[48] Initial results of this longitudinal study suggest that aggressive monitoring and treatment should be used for chronic otitis media with effusion, to maintain normal hearing.

Guidelines recommend that ophthalmological assessments in infants with Down's syndrome should begin at birth—or no later than 6 months of age—to identify congenital cataracts and other congenital disorders such as glaucoma, although not all clinicians agree.[36,37,49] Ophthalmological disorders increase in frequency with age; about 38% of children less than 12 months of age, and 80% of those aged 5–12 years, have disorders that need monitoring or intervention. The most frequent disorders found in children are refractive errors (35–76%), strabismus (27–57%), and nystagmus

Panel 5: **Management of Down's syndrome**

Evaluation
- Echocardiogram
- Ophthalmological assessment
- Hearing assessment

Prevention
- Obesity
- Periodontal disease

Monitoring
- Coeliac disease
- Thyroid function

Vigilance
- Arthritis
- Atlantoaxial subluxation
- Diabetes mellitus
- Leukaemia
- Obstructive sleep apnea
- Seizures

Other
- Sexuality and reproductive health
- Dermatological problems
- Behaviour problems
- Development

(20%).[49–52] Therefore, ophthalmologic assessments should continue annually, to identify refractive errors that may develop in childhood, and to screen for other disorders—such as lens opacities and keratoconus—that could develop in the second decade or later in life.[52]

Disorders to prevent

Prevention of obesity is an important goal. Individuals with Down's syndrome have reduced resting metabolic rates,[53,54] which contribute to a higher frequency of obesity than in other individuals.[55] Usually, infants with Down's syndrome are light for their height, progress to being proportional, become overweight, and by age 3-4 years are more likely than not to be obese. The use of growth charts for children with Down's syndrome is especially helpful in assessment of whether an early light-for-height growth pattern is abnormal.[56] A lifelong regimen to monitor growth and prevent obesity should begin at 24 months of age, including food selections, behavioural interventions, physical activities, and social activities. In adults, a reduced body-mass index correlates with lifestyle variables, especially satisfaction in friendships and access to recreational and social opportunities.[57] Diet should be planned to favour nutrient-rich foods that are high in fibre, and low in calories and fat. Total calorie intake should be less than the recommended daily allowance, and supplementary vitamins and minerals should be considered. Special attention should be paid to intake of calcium and vitamin D, since adults with Down's syndrome have lower bone densities than controls.[58] A programme of physical activity through adulthood is important for control of weight and good bone density.

In individuals with Down's syndrome, regular dental care has the goal of preventing periodontal disease that is almost universal and thought to be due to aberrations in mouth flora.[59] Routine brushing combined with dental visits every 6 months can prevent periodontal disease and associated tooth loss. Orthodontic problems arise in almost all individuals with Down's syndrome. To correct these problems, a child must be able to be co-operative and tolerate the discomfort associated with braces and orthodontic procedures, but such behaviour is not always possible.[59]

Disorders to monitor

Coeliac disease and hypothyroidism occur frequently enough that screening is warranted. Unfortunately, these diseases can be present without symptoms, or with symptoms frequently associated with Down's syndrome.

Coeliac disease is an enteropathy that arises in genetically susceptible individuals. It is triggered by the ingestion of wheat, rye, or barley gluten. With the availability of serum antibody assays and paediatric peroral biopsy techniques, the case finding of coeliac disease has increased,[60] and the frequency of coeliac disease could be as high as 4·6–7·1% in individuals with Down's syndrome.[61–64] Although as a group the height and weight percentiles in patients with coeliac disease may be lower than in Down's syndrome patients without coeliac disease, deficits in weight or height on the Down's syndrome growth charts should not be used as the sole indication for testing. Even in individuals with symptoms, a mean delay of 3·8 years has been reported between the beginning of symptoms and diagnosis of coeliac disease.[64]

Whether all individuals with Down's syndrome should be screened for coeliac disease, and whether a sole screen for coeliac disease at 24 months of age (recommended by the Down's Syndrome Medical Interest Group) suffices for a lifetime, are controversial.[37] As evidence grows that the incidence of coeliac disease among individuals with Down's syndrome is high, unanimity about the need to screen all individuals with Down's syndrome for coeliac disease is likely.

Screening for thyroid disease at birth, at 6 months of age, and yearly thereafter with tests for thyroxine and thyroid stimulating hormone (TSH) is the standard of care. The signs and symptoms of hypothyroidism can develop slowly over time and can be difficult to discriminate from those of Down's syndrome itself.[65] One in 141 newborns with Down's syndrome has persistent primary congenital hypothyroidism, compared with one in 4000 in the general population.[66] The cause of congenital hypothyroidism does not seem to be thyroid agenesis, since most patients have normal thyroid scans.[67] All guidelines recommend yearly screening for thyroid disease, since the frequency increases with age, and is reported to be greater than 15% in individuals with Down's syndrome.[36]

Generally, individuals with a normal to marginal concentration of thyroxine, associated with a TSH concentration of greater than 10 mU/L, are judged to have compensated hypothyroidism and treatment is initiated.[68] However, controversy remains as to whether all such individuals should be treated.[69] No findings have clarified the appropriateness of checking thyroid antibodies to decide whether or not to treat persisting borderline-abnormal TSH. In a 5-year longitudinal study of 101 children with Down's syndrome, Selikowitz[70] found no differences in growth and development between those with slightly raised TSH, showing compensated hypothyroidism, and those with normal TSH. In a longitudinal study of thyroid function in 85 individuals aged 25 years or younger, Karlsson and colleagues[65] treated 30 individuals with mildly or substantially raised TSH, who had a low or marginally low concentration of free thyroxine and had symptoms associated with hypothyroidism; they reported an increase in growth velocity in seven patients. Discussion and additional data are needed to resolve the controversy.

Disorders that require vigilance

Many disorders, such as arthritis, atlantoaxial subluxation, diabetes mellitus, leukaemia, obstructive sleep apnoea, and seizures, occur more frequently among individuals with Down's syndrome than in the general population, but not frequently enough to warrant routine monitoring procedures.

A juvenile rheumatoid arthritis-like arthropathy occurs in 1·2% of children and adolescents with Down's syndrome.[21] Since the mean time from onset of symptoms to diagnosis is 3·3 years (range 3 months to 9 years) in these individuals, compared with 0·7 years for other children, vigilance is called for. In Down's syndrome, the disease is associated with joint subluxations, and with dislocations of the cervical spine, patella, and other joints in 55% of those with arthiritis.[72] The clinical relevance of the slightly raised concentrations of uric acid in the serum of most individuals with Down's syndrome is unclear.[73] However, Down's syndrome with coexistant gout has been reported, and the frequency of this problem could rise as life expectancy for people with Down's syndrome increases.[74]

In children with Down's syndrome, screening for and management of subluxation of the cervical spine is controversial.[75,76] Excessive mobility of the articulation of the atlas (C1) and axis (C2) is termed atlantoaxial

instability. The recommended method for detecting atlantoaxial instability has been a lateral neck radiograph in neutral, flexion, and extension. Individuals with an atlanto-dens space of more than 4·5–5·0 mm are judged to have subluxation with or without symptoms. Reports of poor radiological and interobserver reliability[77] have led some investigators to conclude that these radiographs are "of potential but unproven value in detecting patients at risk for developing spinal cord injury during sports participation".[78] About 13% of individuals with Down's syndrome have an increased space but are asymptomatic. An additional 2% of individuals with Down's syndrome develop signs and symptoms of spinal cord compression, such as a change in gait, loss of bowel or bladder control, hyperreflexia, neck pain, torticollis, quadriparesis, or quadriplegia. Several follow-up studies of children with asymptomatic atlantoaxial instability have shown no development of clinical symptoms, with and without restrictions of specific activities that are thought to place the children at risk of symptomatic disease.[79,80] This finding raises questions about restriction of activities in individuals with asymptomatic disease and the effectiveness of the present screening process. Unfortunately, in many patients, the symptoms of atlantoaxial instability remain unrecognised for weeks and years, making reversal unlikely.[78] Management of individuals with symptomatic subluxation requires immediate stablisation and consideration of surgery. Unfortunately the outcome of surgical stabilisation is often unsatisfactory.[81,82]

Diabetes mellitus develops in at least 1% of children and adolescents with Down's syndrome.[83] Although regular assessment for diabetes is not indicated, prompt consideration of the diagnosis is indicated in the presence of signs and symptoms of diabetes.

Individuals with Down's syndrome are more likely than other children to have some haematological aberrations and disorders. These include polycythaemia in newborns (64% of those with Down's syndrome),[84] macrocytosis (66%),[85] transient myeloproliferative disorder, acute myeloid leukaemia, and acute lymphoblastic leukaemia.[86]

Transient myeloproliferative disorder is a form of self-limited leukaemia that, for unknown reasons, regresses spontaneously by the age of 2–3 months. It arises almost exclusively in neonates with Down's syndrome and occurs in almost 10% of such neonates. The management of this disorder is conservative, and consists of watchful waiting or supportive care. Some affected children later develop myelodysplastic syndrome, or, more frequently, acute megakaryoblastic leukaemia, usually between the ages of 1 and 3 years. For the first several years of life, infants with a history of transient myeloproliferative disorder warrant vigilance and complete blood counts.[86]

Although acute lymphoblastic leukaemia was previously estimated to arise about four times more frequently than acute myeloid leukaemia (most often acute megakaryoblastic leukaemia) in Down's syndrome, the two diseases are now thought to develop with equal frequency (1 in 300).[86] In Down's syndrome, acute myeloid leukaemia arises at between 1 and 5 years of age (median 2 years). Between 20% and 69% of patients with acute myeloid leukaemia and Down's syndrome present with myelodysplastic syndrome, characterised by months of worsening thrombocytopenia followed by anaemia. Patients with Down's syndrome, treated for acute myeloid leukaemia following treatment protocols do better than those who receive no treatment or minimum treatment.

Although myelodysplastic syndrome and acute megakaryoblastic leukaemia are distinct diseases with unique profiles of characteristics in young children with Down's syndrome, the characteristics of acute lymphoblastic leukaemia are the same for children with and without Down's syndrome. Patients with Down's syndrome given standard treatment for acute lymphoblastic leukaemia now have 5-year survival outcomes similar to patients without Down's syndrome, although they tolerate treatment poorly. Molecular studies have not yet provided an explanation for the predisposition for leukaemia in children with Down's syndrome.[86]

Obstructive sleep apnoea is often noted in people with Down's syndrome, probably because of midfacial hypoplasia. Surgical intervention to avoid hypoxaemia and possible cor pulmonale does not always correct the problem. Supplemental or ambient oxygen therapy under pressure in sleep might be indicated, but is not easily tolerated.[87]

In the 8% of individuals with Down's syndrome who develop a seizure disorder, age of onset is bimodal; 40% occur before 1 year of age and 40% occur in the third decade of life.[88] Children develop infantile spasms and tonic-clonic seizures with myoclonus; in adults, partial simple or complex seizures develop.[88] About half of the children with infantile spasms achieve seizure remission without relapse and part restoration of development. In the other 50%, who continue to have seizures,[89,90] there is no difference in outcome between groups treated with valproic acid, corticotropin, or both.[89]

Other medical problems and issues

In adolescent girls with Down's syndrome, the age of onset of the physical features of puberty is similar to that of other adolescents.[91] In boys with Down's syndrome, the primary and secondary sexual characteristics and pituitary and testicular hormone concentrations are similar to those in typical adolescents.[92] Women are able to have children,[84] but men have diminished capacity to reproduce.[93,94]

Clinical guidelines recommend a pelvic examination of women with Down's syndrome who are sexually active or who have menstrual problems. Control of menstrual hygiene may be difficult. A combination of family skill training, a behaviour modification programme, and hormone treatment can be successful. Premenstrual syndrome may present with clusters of temper tantrums, episodes of autistic behaviour, and seizures at (or just before) the time of menses. Patients might respond to treatment with pyridoxine, premenstrual diuretics, low dose birth control pills, or medroxyprogesterone. Sexual education should emphasise responsibility in relation to dating, sexuality, and all relationships.[95] The onset of menopause for women with Down's syndrome is earlier (47·1 years), than for women with mental retardation who do not have Down's syndrome (49·3 years), or for women without mental retardation (51 years).[96]

87% of children with Down's syndrome develop a skin disorder associated with the syndrome, such as palmoplantar hyperkeratosis (40·8%), xerosis (9·8%), seborrhoeic dermatitis (30·9%), fissured tongue (20%), geographic tongue (11·2%), and cutis marmorata (12·6%).[97] By adolescence, dermatological problems frequently cause difficulties, especially folliculitis, which develops in 50–60% of adolescents with Down's syndrome.[98] Skin problems that are especially troublesome in adolescents and adults with Down's syndrome include atopic dermatitis, fungal infections of the skin and nails, seborrhoeic dermatitis, and xerosis. These problems can be responsive to standard treatments, but the fungal

infections especially can be severe and more intensive treatment may be necessary. The autoimmune disorders vitiligo and alopecia both arise more frequently in individuals with Down's syndrome than in the general population.[99]

Individuals with Down's syndrome have been described as having Chaplinesque gait with external rotation of the hips, knees in flexion and valgus, and tibias externally rotated. In childhood, pes planovalgus with marked pronation of the foot create problems with stable ambulation. In the adolescent and adult with Down's syndrome, ambulation may be compromised by severe hallux valgus and hammer toe deformities as well as plantar fasciitis, fatigue, and early onset of pedal arthritis associated with severe flat feet.[100] Management may include consultation with an orthopedic specialist or a podiatrist.

Development, behaviour, psychiatric disorders, and Alzheimer's disease

Individuals with Down's syndrome have a wide range of function in all areas of development. Although in early infancy they function in the range of low typical development, the intelligence quotient decreases in the first decade of life; in the adolescent years cognitive function reaches a plateau that continues into adulthood.[101] Learning can be complicated by a counterproductive style that includes avoidance strategies when faced with cognitive challenges.[102] Although all domains of development follow the usual sequence, a deficiency in language production relative to other areas of development often causes substantial impairment.[103]

Individuals with Down's syndrome have more behavioural and psychiatric problems than other children, but fewer than other individuals with mental retardation. 17·6% of individuals with Down's syndrome aged less than 20 years have a psychiatric disorder, most frequently a disruptive behaviour disorder such as attention deficit hyperactivity disorder (6·1%), conduct/oppositional disorder (5·4%), or aggressive behaviour (6·5%). 25·6% of adults with Down's syndrome have a psychiatric disorder, most frequently a major depressive disorder (6·1%) or aggressive behaviour (6·1%).[104] The dual diagnoses of Down's syndrome and autism has gained much attention; although the association has always been appreciated, recent reports suggest a frequency as high as 7%[105] and great delays in diagnosis.[106,107]

In adults with Down's syndrome, neuropathological changes typical of Alzheimer's disease usually develop by the fifth decade of life. Clinical signs and symptoms of Alzheimer's disease are noted in 75% of such individuals over 60 years of age, and are most frequently seizures (58%), change in personality (46%), focal neurological signs (46%), apathy (36%), and loss of conversational skills (36%). In any adult for whom the diagnosis of Alzheimer's disease is being considered, a complete medical assessment should be done[108] to detect any treatable disorders such as thyroid disease or depression.[109]

Alternative treatments

For decades, nutritional interventions have been popular but controversial treatments for Down's syndrome. Clinical trials of nutritional supplements have had methodological problems and have shown no efficacy.[110] Theoretically, antioxidants may improve some of the clinical problems associated with Down's syndrome. Evidence links oxidative stress with immune dysfunction, malignancy, mild to severe learning disabilities, and premature ageing. In Down's syndrome, the activity of superoxide dismutase, a key enzyme in the metabolism of oxygen-derived free radicals, is increased. This increase could alter the normal steady state equilibrium of reactive oxygen species, leading to oxidative injury. Findings of studies in trisomic mice and in individuals with Down's syndrome provide further evidence of increased oxidative stress.[110] There are ongoing treatment trials of antioxidants in Down's syndrome.

The medication that has received the most interest for the treatment of cognitive problems in Down's syndrome is piracetam. This drug belongs to the group of medications thought to enhance cognitive function in instances of brain dysfunction. In Canada, researchers studied 25 children 6·5–13 years of age with Down's syndrome treated with piracetam in a double-blind crossover trial. Tests of attention, learning, and neurocognitive function showed no consistent beneficial cognitive effect versus placebo. However, seven of 18 children who completed the study had associated central nervous system stimulatory effects including aggressiveness (four children), agitation (two), sexual arousal (two), poor sleep (one), and decreased appetite (one).[111]

Epidemiology of life expectancy

In the past decade and a half, investigators in many countries have noted a substantial improvement in the median age of death in individuals with Down's syndrome.[112] In a survey of 17 897 individuals with Down's syndrome compiled by the US Centers of Disease Control and Prevention National Center for Health Statistics for 1983–97, the median age of death increased from 25 years in 1983 to 49 years in 1997 ($p<0·0001$).[113] When assessed by racial group, the median age of death was significantly higher in white people than in black people and people of other races. On the basis of data from death certificates, standardised mortality odds ratios (SMOR) of people with Down's syndrome were more likely to show congenital heart defects (SMOR 29·1), dementia (21·2), hypothyroidism (20·3), or leukaemia (1·6) than those of people without Down's syndrome. Apart from leukaemia and testicular cancer, the SMORs for malignant diseases associated with Down's syndrome were low.[113]

Although children are at increased risk of leukaemia, individuals with Down's syndrome have a reduced risk of solid tumors in all age-groups.[114] When the longevity of people with Down's syndrome is compared with that of those with mental retardation in general, functional predictors of survival do not differ. In children aged less than 11 years, the main predictor of poor survival is being non-mobile or fed by tube; whereas among those aged 11–39 years, ambulation was the best predictor of survival.[115] These data relate to the population in the USA; other countries might show different patterns.

Counselling and psychosocial issues

Many different disciplines and physician specialists participate in counselling parents about a child with Down's syndrome. They discuss prenatal screening, newborn diagnosis, health issues, informative publications,[116-125] parent groups, advocacy, educational choices, employment, and transitions to adult living opportunities. The quality of guidance and the way in which it is presented are very important. Fortunately, most experienced professionals have worked with individuals with Down's syndrome, since such children

are easily identified and enter the system early in their life. In the USA, about 30–40 years ago, children with Down's syndrome were often referred at birth to residential institutions. During the past 20 years, trends have developed for entrance into the early intervention educational system within the first few months of life to stimulate development, inclusion in the typical classroom with support, and help for employment and adult living situations. Planning for these successful outcomes depends on the development of abilities to complete tasks without assistance, a willingness to separate emotionally from parents, and access to personal recreational activities.[126,127]

Conclusion

Most of the positive improvements in the quality of life of people with Down's syndrome are the result of parental support. Typically, parents are disappointed when their newborn is diagnosed with Down's syndrome. However, within a few months, they become attached. Parents frequently report that the child with Down's syndrome is happier and more loveable than other children, although investigators have found children with Down's syndrome to be of similar temperament to other children. Clearly, many individuals with Down's syndrome lead satisfying, productive lives and are a source of pride and comfort for their families.

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