

Adults with Down syndrome – health/care considerations for health professionals

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Acknowledgements: the authors thank prof. dr. J. Lebeer (University of Antwerp, Faculty of Medicine and Health Sciences, Department of Handicap Studies) who, as promoter of the master thesis of Catharina Elsing and Simone van der Ent, contributed to the realization of the Downpas 18+ .

Keywords:

Down syndrome, premature ageing, health problems, medical follow up

Abbreviations:

A β : Amyloid- β - AD: Alzheimer disease - APP: Amyloid precursor protein - BMI: Body mass index - CNS: Central nervous system - DS: Down syndrome
OSAS: Obstructive sleep apnoea syndrome

Introduction :

Life expectancy in Down syndrome (DS) has increased from 12 years in 1949 to more than 55 years at present [1,2,3]. Consequently, there is an increased need for specialized health care in DS adults [4]. These adults are more at risk for specific health problems that require appropriate screening and follow-up [5,6]. Common and major health problems include central nervous system pathology (dementia, seizures), visual and hearing impairments, hormonal problems (thyroid dysfunction, diabetes mellitus, premature menopause), gastrointestinal disorders, obesity, cardiovascular pathology, sleep apnoea and musculoskeletal problems, as well as dermatological and immunological changes [7].

There is a speculation that trisomy 21 could affect gene/protein expression, resulting in increased oxidative stress and impaired mitochondrial function [8]. This would lead to premature ageing in DS [9,10,11]. Premature ageing accounts, at least in part, for several observed health risks in adults with DS. On the other hand, some frequent health problems are not restricted to DS but are common to other adults with intellectual disability [12,13].

This review focuses on the rates and contributing factors to common DS-related medical conditions in adults and their changes with age. We studied the scientific literature on DS and common health problems. For many disorders, the number of studies is limited. Furthermore, different studies were apparently conducted by the same researchers. Prevalence rates of a specific disorder can be highly variable between studies. This may be due to variable definitions or diagnostic criteria of a particular disorder, to selection bias or variations of the studied population samples. Some studies date from several decades ago while over the last 2 decades, life expectancy has still further increased. This also partly explains large differences between recent and older studies. Some studies have been published

in textbooks or in low impact factor journals. In spite of methodological limitations, the results of research studies on health in DS adults allow the development and presentation of reasonable guidelines for screening and follow-up of this still enlarging group of patients [14].

Central nervous system

Neurobehavioral disorders :

Prevalence estimates of neurodevelopmental and psychiatric co-morbidity in DS children range from 18 to 38% [15,16]. Most problems will persist into adulthood as these include autism spectrum disorders, childhood psychosis, conduct disorder, emotional disturbance, and hyperactivity disorder [15,17,18,19,20].

Up to 10% of DS adults present with depression, with a mean onset at age 29 years. Psychosocial stressors may precede the onset of mood disorders. Also obsessive-compulsive disorder and disorders with psychotic features are common after puberty. On the other hand, mental illness is less common than in other adults with intellectual disability [21,22]. Daytime fatigue or somnolence should raise the suspicion of a sleep disorder like obstructive sleep apnoea syndrome, rather than psychiatric illness [23]. In addition, depression should always be differentiated from dementia.

Epilepsy

About 8% of DS individuals experience a seizure throughout life with an age-increased prevalence reaching 46% after 50 years [24,25]. In general, seizure occurrence follows a bimodal distribution with a first peak in the first two decades of life and a late-onset peak around the 5th-6th decade [26,27]. While in the younger

age group primarily infantile spasms and tonic-clonic seizures are observed, older individuals display more often simple partial seizures or complex partial seizures besides tonic-clonic seizures [28,29,30]. Late-onset myoclonic epilepsy is likely underreported in view of the recently increased life expectation [31,32,33,34]. Late-onset seizures can be a sign of Alzheimer disease [35].

Dementia and Alzheimer disease

Adults with DS are highly at risk for early-onset dementia. Together with depression, AD is the major health problem in ageing DS individuals. By 35-40 years of age, all DS individuals show neuropathologic features of AD on autopsy. However, these changes do not always result in clinical dementia [36,37]. Intellectual disability may influence the clinical diagnosis resulting in large differences of estimated prevalence rates of AD in DS. AD prevalence increases with increasing age of DS individuals, e.g. in one study from 8% between 35 and 49 years, up to 75% after 60 years of age [38].

Triplification and overexpression of the amyloid precursor protein gene (APP), located on chromosome 21 could at least partly explain increased levels of amyloid- β (A β) peptides and the nearly universal presence of AD neuropathology. APP overexpression contributes to accumulation of diffuse extracellular deposits of A β in the DS brain during the second and third decade and subsequent formation of fibrillar plaques by the end of the fourth decade. Large individual differences in plasma A β levels and the wide onset range of AD suggest a more complex pathogenesis of AD in DS [35,39]. Modifying factors like apolipoprotein E epsilon4 allele, oestrogen deficiency and high levels of A β 1-42 peptide are associated with earlier onset of dementia in DS [37,40]. For example, females have an earlier onset and a more severe form of AD, even more in case of an early menopause onset (< 46 years) [41,42].

Dementia in DS usually has an early onset and is rapidly progressive. Although neuropathology shows abnormalities typical of AD, the first symptoms are related to behavioural changes and social dysfunction, which in a non-DS individual would be more suggestive of frontotemporal dementia ("Pick's dementia") rather than AD [43,44,45]. The first cognitive sign in DS, visual memory loss, is followed by impaired learning capacity and loss of occupational skills. Typical cognitive deficits are impairments in morphosyntax, verbal short-term memory, and explicit long-term memory. However, visuospatial short-term memory, associative learning, and implicit long-term memory functions are preserved [46]. There is no useful clinical or laboratory test for AD in DS [47].

Specific psychological tools designed to measure cognitive decline in persons with intellectual disability are available like the Dementia Questionnaire for Persons with Mental Retardation [48] and the Dementia Scale for DS (DSDS) [49]. Many similar tests are however not sufficiently validated, including the Test for Severe Impairment [50] and Severe Impairment Battery. Standard tests for use in the general population (e.g. the Mini Mental State Examination) do not apply [51]. Furthermore, knowledge of previous adulthood assessments of cognitive function is essential for comparison with the measurements in the symptomatic stage. In spite of attempts to construct consensus diagnostic criteria for AD in DS [52], psychological evaluation can actually merely establish suspected cognitive decline, but it cannot not make a diagnosis of AD since other causes than AD may be responsible for the observed cognitive decline. Hence, it is most important to rule out other health problems, which include depression, OSAS, hypothyroidism, diabetes mellitus, vitamin deficiencies, infections, chronic intoxications (e.g. antiepileptic drugs) and impairment of hearing or vision. Obviously, diagnosis of AD in its early stage becomes more difficult with a more severe pre-existent intellectual disability and it is often impossible to distinguish between depression and dementia. In spite of financial and practical obstacles, we recommend repetitive measurement of cognitive function from the age of 40 years.

At a later stage, seizures and urinary incontinence occur, as well as deterioration of speech and motor function due to apraxia, resulting in gait disorders [53]. Self-care abilities gradually disappear. Patients become bedridden, and they depend for nourishment on caretakers. They may eventually survive years in a vegetative state (particularly in case of gastric tube feeding) until brainstem degeneration affects vital functions [54].

Cognitive decline is apparently more marked in demented individuals suffering from seizures [55]. In DS individuals over age 45 years, those with seizures are more prone to dementia [56] and seizures can also be a diagnostic clue to AD [35]. The mechanisms relating seizures to cognitive decline in DS are not clear but high brain levels of A β may disturb normal synaptic and other neuronal activity [55]. Seizures eventually occur in 84% of individuals with DS and AD [38].

Vision and Hearing impairment

Vision impairment is more prevalent in DS, with severe impairment in up to 45% of DS individuals above 50 years old. Common problems are cataract (11-33%), strabismus (23-37%), refraction problems (30-34%) and keratoconus (15%) [57]. In parallel with the accelerated aging process, cataract develops earlier in DS [58].

Similarly, age-related hearing loss is more common among DS adults (prevalence 12-72%) compared to the general population, with an earlier age of onset [57,59,60]. High frequency sensorineural hearing impairments (such as presbycusis) starts about 30 to 40 years earlier than in the general population [61]. Also chronic and inadequately treated middle ear infections in childhood may have an impact on later hearing loss in adults with DS. One study of a DS adults sample characterized hearing loss as conductive in 10%, sensorineural in 45% and mixed in 44% [57].

Impairments of vision and hearing diminish daily functioning and require early diagnosis and treatment. Both lead to behavioural changes and can be confounded with AD. Lifelong surveillance is therefore necessary with repeated assessment of the vision and hearing function at least once every 2 years.

Sleep apnoea

Obstructive sleep apnoea syndrome (OSAS) is common in DS and may lead to pulmonary hypertension and cor pulmonale. The scarce studies examining the incidence of OSAS report up to 94% of DS adults suffering from this disorder [23]. The relative underdevelopment of the midface, sometimes associated with a narrow nasopharynx, glossoptosis, superficially positioned tonsils, tonsillar and adenoidal hypertrophy, and the high rate of hypotonia are the main reasons for the high incidence. Additional risk factors are obesity and hypothyroidism. Suspicion for OSAS should be raised if parents or caregivers note an unexplained fatigue, an unusual sleeping position, significant snoring or restless, disturbed sleep with awakenings. A polysomnography may help to clarify concerns about sleep apnoea and specialized ENT advice on the cause and possible treatment of sleep apnoea is necessary.

Oral health

The hypotonia of the tongue and lips may hinder mastication and swallowing thereby contributing to a reduced "self-cleansing" of the mouth and hence an increased accumulation of food debris and dental plaque [62]. In addition, mouth breathing may also contribute to an increased accumulation of dental plaque and reduces the protective function of saliva, which may predispose to dental caries. Furthermore, enamel hypoplasia and hypocalcification are also phenomena more often observed in DS. As these defects make teeth more vulnerable for dental caries, extra preventive measures (e.g. fluoride applications) are indicated [63,64,65,66].

Individuals with DS experience a significantly higher prevalence of periodontal disease (not only gingivitis but also destructive periodontitis), at a younger age and in more severe forms than in the general population [66,67]. The progression of the periodontal breakdown is much higher and the decreased root lengths may also contribute to a more rapid loss of teeth [68]. The exact cause remains unknown, but altered immune response mechanisms and particular periodontopathogenic bacteria and viruses are suspect [67,69,70,71]. Daily oral hygiene, a healthy diet and regular dental visits (including professional debridements) are of utmost importance in all DS individuals.

Endocrinological problems

Thyroid gland

A high incidence of thyroid dysfunction in DS has been reported [72,73,74] and includes congenital hypothyroidism, primary hypothyroidism, auto-immune (Hashimoto) thyroiditis, compensated hypothyroidism and even hyperthyroidism (Graves disease) [75]. Although clinical findings of thyroid disease are not different in DS, the DS phenotype may mask typical findings of hypothyroidism, like increase in weight, dry skin, constipation and lethargy. Consideration of hypothyroidism is also mandatory in the differential diagnosis of depression and dementia.

The natural history of thyroid function in adults with DS is relatively unknown with limited long-term follow-up data. Prasher et al performed annual thyroid function tests in 200 DS adults during 10 years [72]. Five and 10-year incidence of hypothyroidism was 1,64% and 13,6% respectively. Interestingly, subclinical hypothyroidism was not found to be an early sign for later development of clinical

hypothyroidism. Recently extended follow-up to 15 years confirmed that the majority of adults with DS do remain euthyroid. Based on these findings, Prasher et al. suggest thyroid screening every 5 years [76]. As it is still a matter of debate we currently recommend thyroid function testing every 2 years independent of the previous thyroid status (See table 1).

Diabetes mellitus

Type 1 diabetes mellitus has a considerably high prevalence (1,4-10,6%) in DS children, with a peak onset at 8 years [77], and remains a major concern in adulthood with its typical comorbidity. In contrast, a preliminary report looking at type 2 diabetes reported a lower incidence [78]. As these data need to be confirmed, we recommend to check plasma glucose levels every 2 years.

Sexuality

Sexual activities, including intercourse, are not rare in adults with DS. Defective spermatogenesis would be responsible for male infertility in DS. However, infertility may be overestimated in view of the developmental delay and associated social obstacles to procreation. To date, the literature reports three men with DS who became father [79] and almost 50 cases of established female fertility [80]. DS occurs in 50% of offspring of DS mothers [80]. Therefore, DS adults need information and medical care concerning sexuality, reproduction, contraception and sexually transmitted diseases [81] and in addition examination of the cervix by Papanicolaou (Pap) smear is recommended every 1-3 years in sexually active women [7, 82,83].

Menopause in DS women appears at a mean age of 44 years, compared to 51,4 years in the general population [84,85,86]. Since earlier menopause and postmenopausal oestrogen reduction may contribute to earlier onset and increased risk of Alzheimer disease [42,87] and to increased mortality [87], specific medical attention for dementia after menopause is needed. Finally, the association with AD and increased mortality might explain male predominance among elder DS patients [88].

Gastrointestinal system

DS-related hypotonia and connective tissue laxity are the most probable explanations for the high prevalence of functional gastrointestinal problems (gastro-oesophageal reflux disease, functional constipation) and hernias (up to 20%) in DS adults [58]. Although probably more prevalent in DS children, celiac disease can initiate at adult age. According to the literature testing for celiac disease in adults would only be warranted in case of suggestive symptoms (diarrhoea or constipation, abdominal distension, fatigue, irritability or anaemia)[5]. Some authors and guidelines suggest HLA DQ2 and HLA DQ8 typing in the first year of life in order to investigate whether a given patient is susceptible to develop CD or not [89] (See also article E. Maris in this issue [90]). Further studies are needed to evaluate if adults may benefit from a more systematic screening. Besides celiac disease, hypothyroidism must be ruled out in case of chronic constipation in adults.

Overweight/obesity

Overweight/obesity is a common concern among DS individuals, occurring in 45-79% of males and 56-96% of females. Contributing factors are a combination of eating behaviour and reduced exercise [91]. As a consequence, special attention is needed regarding the diet and physical activity in individuals with DS. Thyroid function should be routinely checked in those with unexplained weight gain.

Cardiovascular problems

Congenital heart disease occurs in 30-60% in DS, requiring corrective heart surgery at young age and continued regular cardiac follow-up throughout life. If left untreated, pulmonary hypertension will develop at a young age leading to significant morbidity and/or precocious death [58].

Even if no cardiac disease is diagnosed at a young age, DS adults are at risk for valve dysfunction, mainly mitral valve prolapse (up to 57%) and aortic regurgitation (up to 17%) [92,93]. Mitral valve prolapse is mostly asymptomatic or may present with fatigue, weight gain and irritability. Endocarditis prophylaxis prior to dental or surgical procedures is necessary in case of valve disease [5,83]. Therefore, a cardiac evaluation at the age of 18 years is advised.

Given the characteristic premature ageing seen in DS, one might expect also a premature formation of atherosclerotic plaques at the vascular level. In contrast, several studies indicate that DS adults with DS are protected against atherosclerosis. The potential protective mechanisms are not known and merit additional research [94].

Moyamoya disease is a rare occlusive cerebrovascular pathology, but more frequent in DS, particularly in children and young adults [95]. It preferentially affects the supraclinoid internal carotid arteries, resulting in various forms of stroke by formation of tortuous collateral vessels. The pathogenesis is unknown [96].

Respiratory system

Both acute and chronic respiratory tract diseases occur frequently in the adult DS population. Pneumonia and other respiratory infections are a main cause of death in adult people with DS [97]. The high susceptibility for respiratory infections is shown by Van Allen et al. reporting the occurrence of pneumonia in 55,2% of DS adults during follow-up, justifying vaccination against pneumococci [58].

Furthermore, respiratory problems related to aspiration are frequent and can lead to chronic interstitial changes of the lungs. Lower oesophageal sphincter incompetence and gastro-oesophageal reflux disease in patients with neurogenic dysphagia, obesity and a sedentary life-style are the main risk factors [58,98].

Musculoskeletal system

Approximately 20% of people with DS have musculoskeletal disorders [99]. Musculoskeletal problems often result from reduced muscle strength and premature degenerative bone and joint disease [100,101,102,103]. Osteoporosis is common among adults with DS [104]. Potential contributing factors are early menopause, decreased physical activity, low muscle tone and decreased strength, and anticonvulsant medication [105]. Degenerative osteoarthritis is also common among adults with DS and degenerative changes of the spine affect 22% of middle-age adults and 40% of elderly adults [58]. Other orthopaedic problems are mostly related to the generalized laxity of the connective tissues and hypotonia of the muscles. They include upper cervical spine instability (incidence 10-15%) [106], scoliosis (range 8,7-52%) [107,108], hip problems (range 1,25-7%) [107,109,110], patellofemoral instability (20%) and foot disorders (metatarsus prima varus and pes planus) [111].

Skin and hair changes

Different dermatological disorders are associated with DS. Most common are xerosis, atopic and seborrhoeic dermatitis, palmoplantar hyperkeratosis and alopecia areata. They often represent a challenge to treat and important to note is that generalized xerosis could be easily misinterpreted as atopic dermatitis. Other dermatological manifestations almost exclusively occurring in DS are milia-like calcinosis cutis, mostly on hands and feet, and syringomas of the eyelids [112]. Cutaneous bacterial (folliculitis, furuncles, abscesses and impetigo) and fungal infections (onychomycosis and tinea pedis) are also frequent in DS [113,114]. Accelerated ageing leads to premature greying of the hair, hair loss and wrinkling of the skin [80].

Urinary tract disorders and impaired renal function

Recurrent urinary tract infections occur in more than 25% of DS adults, particularly in those who are bedridden [58]. Slightly impaired glomerular filtration probably reflects premature ageing of the kidneys. Different renal anomalies have also been reported in DS [115,116,117,118]. Said et al. reported a wide range of glomerular lesions in relatively young DS adults, predominantly IgA nephropathy and focal segmental glomerulosclerosis [119]. This finding justifies regular monitoring of renal function and urine sediment in DS adults. However, in the study of Malaga et al. the incidence of renal failures in the DS population did not differ from the incidence within the rest of the population [118].

Immunological problems

Although older DS people display a higher susceptibility to infections, most individuals with DS do not show clear features of immunological diseases. Premature ageing of the immunological system has been suggested by Trotta et al. [120]. Immunizations are recommended for all adults. After receiving the usual immunizations of childhood, a diphtheria-tetanus booster is recommended every ten years. DS individuals with chronic cardiac and respiratory disease or individuals older than 50 years are candidates for use of pneumococcal and influenza vaccines. Hepatitis B immunization is recommended in residential facilities [82].

Patients with DS have an increased risk for several auto-immune diseases, including auto-immune thyroiditis, celiac disease, diabetes mellitus type 1, alopecia and vitiligo. Frequently, the occurrence of an auto-immune disease in a patient predisposes to the development of another one [121].

Haematological and oncological problems

Although associated at younger ages, no increased risk for leukaemia is reported after the age of 40 [122].

Solid tumours are infrequently reported in patients with DS. The reduced risk of developing solid tumours in DS individuals, including breast tumours in females, occurs across the life-span, with no significant change with age [123]. The proposed screening guidelines for breast cancer in DS women however, are the same as in the general population [124].

The risk for testicular cancer, particularly testicular germ cell tumours with predominance of seminomas, has been reported to be higher in DS [125,126]. Currently, the mechanism of increased risk is not well understood. Cryptorchidism and hypogonadism have been implicated as risk factors. Testicular tumours can occur at very young ages and close surveillance of the gonads of male patients with DS is critical. An annual testicular examination is recommended [7].

Social independence

Dependency in daily skills, such as feeding, washing, dressing and toileting remains in a significant proportion of adults with DS. Fewer than one-half of young adults are independent in all four. Other authors report competencies of 80% to over 90% in these domains [127]. Social independence in adults with DS depends largely on the development of abilities to complete tasks without assistance, the willingness to separate emotionally from parents and access to personal recreational activities [128].

The Downpas 18+

The "Downpas" is a Flemish health diary for children with DS. In consequence of its success in Flanders, the authors recently developed a "Downpas 18+". The "Downpas 18+" focuses on the health risks for adults with DS. At this moment, the "Downpas 18+" is in its experimental phase prior to publication for common use (responsible publisher: Dr. Stephanie Van den Braembussche). In table 1 the Downpas 18+ recommendations for medical follow up of DS adults in Flanders are listed. These recommendations are based on the prevalence of health risks in adults with DS, on suggested guidelines in literature and on the Belgian health care system and services.

Table 1. Recommendations for medical follow up of DS adults (Downpas 18+)

Schema 18+	Frequency follow up (FU)
General clinical examination	Annual, FU weight
Blood tests	Every 2 years: plasma glucose, total blood count, thyroid function (TSH, FT4, thyroid antibodies), renal function
Central nervous system	Ask for behaviour problems
After 40 years: assessment of dementia every 3 years (between 20-30 years: measuring 'zero' level)	
Vision testing	Every 2 years
Ear/hearing examination	Annual otoscopy (removal ear smear)
At least every 2 years audiometry	
Oral care (dental visit)	(at least) Twice a year
Obstructive sleep apnea syndrome (OSAS)	Ask for OSAS symptoms every year
Heart	Evaluation at 18 years for mitral valve prolapse, especially prior to dental and surgical procedures. ECG and echocardiography every 5 years. In case of congenital heart defect: follow up on indication
Musculoskeletal system	Annual clinical examination for atlanto-axial instability. Evaluate for symptoms of degenerative osteoarthritis and consider osteoporosis especially after menopause

Gastrointestinal system	Ask for celiac disease symptoms, if suggestive test anti-tissue transglutaminase Ig A antibodies and (once) total IgA. In IgA deficient patients, anti deaminated gliadin IgG is used for screening.
Kidneys	Every 2 years: urinary sediment and renal function in blood
Gynaecological follow up	Pap smear every 1-3 years in sexually active women. Breast cancer screening after 50 years: general guidelines
Testicular follow up	Annual clinical examination

Conclusion

Life expectancy in Down syndrome has significantly increased due to improved medical care. Ageing adults with DS are at risk for a wide spectrum of specific health problems and they are hence in want of a more specialised care. For the group of children with DS multidisciplinary settings (Down syndrome specific consultations) already exist in Belgium. Special needs of DS children can be addressed by consultant paediatricians who can coordinate prevention, follow-up and early intervention in a multidisciplinary setting like a DS Team. Currently, follow-up of DS adults is mainly done by general practitioners. However, in regard of all the possible health problems in DS adults, this may be a too difficult task for a single physician. Ideally, follow-up of DS adults should be organised in the same manner as for DS children. Besides specific guidelines and recommendations, a training program for physicians dedicated to the care of DS adults is needed. Contrary to the Netherlands, a specific training program for the medical care of persons with intellectual disability do not exist in Belgium at the present time. The authors hope that the Downpas 18+ can at least partly help to overcome these structural obstacles to appropriate care for the DS adult. Further actions and policies are needed to improve health and quality of life of this enlarging group.

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